Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Forty-Five Years With a Hydra, Organosulfur Chemistry

Lamar Field[a]
[a] Department of Chemistry, Vanderbilt University, Nashville, TN, USA

To cite this Article Field, Lamar(1993) 'Forty-Five Years With a Hydra, Organosulfur Chemistry', Journal of Sulfur Chemistry, 13: 2, 197 — 272
To link to this Article: DOI: 10.1080/01961779308048956
URL: http://dx.doi.org/10.1080/01961779308048956

Sulfur Reports
Volume 13/2, pp. 197–277
Photocopying permitted by license only

FORTY-FIVE YEARS WITH A HYDRA, ORGANOSULFUR CHEMISTRY

LAMAR FIELD
Department of Chemistry, Vanderbilt University, Nashville, TN 37235, USA

(Received September 7, 1992)

Lamar Field was born in 1922 in Alabama, USA. After attending public schools there, he entered M.I.T., where he received a Rogers Award to outstanding seniors and from which he received the S.B. degree in chemistry in 1944. After two years in classified research at Merck and Co. during World War II, in 1946 he returned to M.I.T. At M.I.T., he taught classes as an Advanced Teaching Fellow, was a lecture demonstrator, and then held the Socony Fellowship. After graduation in 1949 with a Ph.D. in organic chemistry, he joined the faculty at Vanderbilt University as Instructor of Chemistry, a rank once common but now strange to the ear. By 1959, he had become Professor of Chemistry and remained so for 30 years, during which he served as department chairman for six years. He has served the American Chemical Society in a number of respects and has served as consultant to the National Institutes of Health, to several industries and to several educational accrediting groups. In 1968, he was Coulter Lecturer at the University of Mississippi and in 1974 was a Fellow at the Australian National University. He is a member of Alpha Chi Sigma, Sigma Xi, and Phi Beta Kappa. In 1989, he became Professor of Chemistry, Emeritus at Vanderbilt. As the Table of Contents shows, the research of the group at Vanderbilt has ranged widely, covering most of the functional groups of organic sulfur chemistry. This account of the research is intended to be mildly provocative in inviting readers to compare their explanations with those published and to pick up the trails in areas where further explorations seem likely to be promising.

Key words: Bioorganic and medicinal-organic sulfur chemistry; derivatives of sulfurous, sulfuric, sulfenic, sulfinic, and sulfonic acids; di-, tri-, and polysulfides; sulfones; sulfoxides; sulfur heterocycles; thiols and thio acids; thiono compounds.

CONTENTS

1. FIRST ENCOUNTERS

One of the twelve labors of Hercules was to kill the Hydra, a monster with nine heads. As each head was struck off, two new heads appeared in its place. Orga-

nosulfur chemistry is a scientific Hydra: each problem solved leads to two more (a colleague wryly remarked that this proliferation is not unique to sulfur chemistry).

My acquaintance with the sulfur Hydra began innocuously enough, when I was freshly out of M.I.T. with an S.B. degree. I was privileged to begin work as a junior chemist in 1944 during World War II, at Merck and Co., to assist John C. Sheehan in the total synthesis of penicillin, which contains sulfur. As John Sheehan has told the story,[1] this project was classified Secret and was equalled as a wartime research endeavor only by the Manhattan Project that led to the atomic bomb; it involved more than a thousand chemists in 39 laboratories in the U.S.A. and Britain, and 90 different proposals of structure were offered. We managed to achieve the total synthesis of a penillic acid ester,[2] an important rearrangement product formed under mild conditions by the acid-catalyzed reaction of a penicillin, but only 13 years later in 1957 did the work of Sheehan and his coworkers at MIT eventuate in the first rational total synthesis of a penicillin.[1] At the end of the war, in 1946, although my fortunate association with John Sheehan impressed me as equivalent to postdoctoral work, it now became necessary for me to do the antecedent doctoral work. My doctoral research, undertaken at MIT under the also cherished guidance of Arthur C. Cope, was intended to involve syntheses and rearrangements that bore no relation to organosulfur chemistry; indeed, as I studied Connor's excellent (and still valuable) chapter on "Organic Sulfur Compounds,"[3] I well recall being appalled by the bewildering array of names and reactions. Sulfur chemistry, I thought, was not for me. Near the end of my work, however, Dr. Cope asked me, as his then research assistant, to add a few odds and ends to prior work on the rearrangement of allylic sulfinates to sulfones, as a prelude to publication of this work.[4] Although the exasperating instability of the sulfinic esters I encountered only confirmed my intention to abstain from sulfur chemistry forever, among many research problems I wanted to study when I became an Instructor at Vanderbilt University in 1949 (hereafter VU), there happened to be one problem that involved sulfonic-acid anhydrides. As fate dictated, I undertook this one first. After that, the organosulfur Hydra engaged my research efforts for the next forty years at VU.

In this summary of work at VU on some fifty classes of organosulfur compounds (most of those known), the organization will be by increasing oxidation level of classes, rather than by chronology. Much of this research was done with the approach of a double-barreled shotgun, one barrel being aimed at basic organosulfur chemistry and the other at biological and/or medicinal applications. The chemistry will be emphasized here, with the biological aspects merely being summarized in Section 16. Where the work of others unconnected with VU is referred to, an effort is made to credit those principally responsible, but the often involved details of the actual references to others must be left to be sought in our paper that is cited.

2. THIOLS

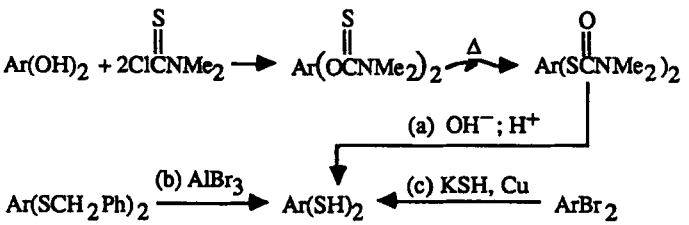
2.1. *Synthesis*

Interest in aryl disulfides (Sec. 5) led us to work with the Leuckart synthesis of thiophenols. The product from this reaction of a diazonium salt and potassium ethylxanthate usually has been assumed to be a xanthate ester (**1**), which then can be hydrolyzed to the arenethiol. Along with the xanthates (**1**) in up to 50% yield, however, we isolated dithiolcarbonates (**2**) in up to 72% yield and, for the first time, ethyl ethylxanthate (**3**) in yields up to 55%;[5] it seems likely that dithiocarbonates

$$ArN_2^+ + EtOC(S)S^- \longrightarrow \underset{\mathbf{1}}{ArSC(S)OEt} + \underset{\mathbf{2}}{(ArS)_2CO} + \underset{\mathbf{3}}{EtOC(S)SEt} \qquad (1)$$

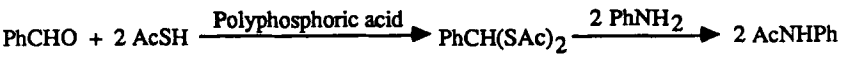
contribute to the yields of thiol previously attributed only to the xanthate. Eq. 1 seems to be general,[5] although the product from the *p*-nitrobenzenediazonium salt turned out to be bis(*p*-nitrophenyl) disulfide rather than the initially presumed nitro dithiolcarbonate.[6] Mechanisms were suggested for the formation of **1-3**, but there is clearly much room for work on eq. 1 and, indeed, on the mechanism of the Leuckart synthesis in general.

A need for an arenedithiol, 2,5-dimercaptoterephthalic acid, led us to compare several means for preparing this dithiol.[7] Scheme 1 illustrates these (where Ar is the dicarboxyaryl group or its ester). Route (a), an extension of the Newman-Karnes synthesis for monothiols worked best (the conditions used for hydrolysis of the amide



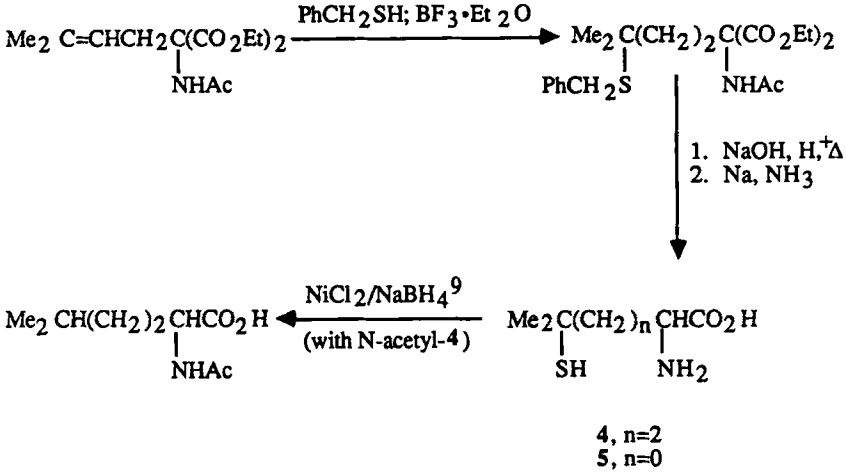
Scheme 1

proved to be critical). Monothiols also were prepared, so the results may provide guides useful for the synthesis of arene mono- and dithiols, as well as for replacement of aryl halogen by SH or SCH_2Ph.[7] *gem*-Alkanedithiols also attracted our interest, and we were able to synthesize a *gem*-dithiol diacetate, as a derivative, from benzaldehyde, but not from cyclohexanone; this thiol acetate acylates aniline readily but not the less basic *p*-nitroaniline (Scheme 2).[8]



Scheme 2

Still other work led to what proved to be the best means at the time of catalyzing a Markownikov-type addition of a thiol to an alkene, i.e. by use of $BF_3 \cdot Et_2O$ (Scheme 3);[9] the saponification and debenzylation shown in Scheme 3 gave a bishomolog (**4**) of penicillamine (**5**), which allows one to determine by comparison whether any one of the wide variety of biological and medicinal properties of **5** depends on ring formation involving the SH and NH_2 or only on their independent action (cf. Sec. 16.2).[9] It is worth adding that a desulfurization for proof of structure in this work failed with Raney nickel, perhaps because of too strong an adsorption, but succeeded with $NiCl_2$ + $NaBH_4$,[9] a (more convenient) procedure of Truce and Perry (Scheme 3).[10]



Scheme 3

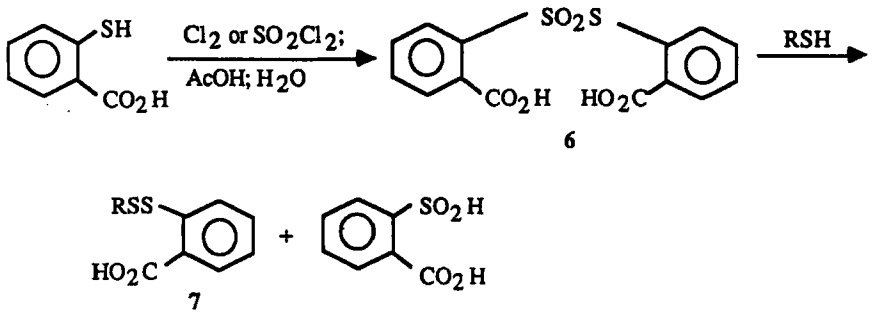
2.2. *Reactions*

Prodrugs are modifications of drugs intended to liberate the drug in the body and thus "to optimize the delivery of an active drug to its site of action while minimizing toxicity and unfavorable reactions to the drug."[11] The possibility of converting medicinally important thiols to prodrugs led us to examine addition products of thiols with carbonyl compounds.[12] It seemed to us that carbonyl compounds that form stable hydrates should be particularly effective. With aldehydes, the equilibrium constant for eq. 2 ranged from as high as ca. $> 10^3$ for

(2)

phenylglyoxal to only ca. 5 for benzaldehyde and ca. 0 for acetaldehyde. With ketones, the range was from ca. 10^3–10^5 for hexafluoroacetone down to ca. 0 for acetone and ethyl acetoacetate. The largest values were indeed for carbonyl compounds known to form isolable hydrates.[12] Where K equaled or exceeded 10^2, the α-hydroxy sulfide could not be converted with a thiol under mild conditions to a mercaptal (thioacetal) or mercaptole (thioketal), but where K was 0–10^2 catalysis with HCl or BF_3 led to the usual well-known reactions of these kinds.[12] As discussed later, several of the α-hydroxy sulfides were isolated and tested as drugs (cf. Entry 8, Table 5).[13] In another approach to prodrugs at VU, a thiol with biological potential was added conjugatively to maleic or cinnamic acid, but release of the thiol did not appear to occur with sufficient ease to lead to useful biological activity (cf. Table 6, Miscellaneous).[14]

The *o*-carboxyphenylthio moiety, *o*-$HO_2CC_6H_4S$, also was promising for converting thiols to prodrugs (cf. Entry 5, Table 5),[15,16] and it occurred to us that the thiosulfonate **6** not only would be useful for such syntheses but also could provide a carboxyl handle useful for isolating, purifying, resolving, or characterizing thiols by conversion to **7** (eq. 3).[17] The thioarylation reaction of eq. 3 proved to be general for a wide variety of thiols (Sec. 5.1), and the disulfides **7** then could be converted either to the parent thiol



(3)

(RSH) or its disulfide (RSSR); as one example of use, **6** completely blocked the SH groups of an enzyme, after which reduction regenerated 95–100% of the enzymatic activity.[17] The various disulfides (**7**) differed nicely in melting points and TLC values and could be titrated.[17]

In other work, the reaction of α-mercapto-α-ethylbutyric acid with chlorine gave H_2SO_4, along with a dichloro-α-ethylbutyric acid (probably the α,β isomer) and α-ethylcrotonic acid; this result may help to clarify the nature of other chlorinolyses.[18] Research with ω-mercaptoalkyl disulfides (Sec. 5.3.3) and sulfoxides (Sec. 10) and some other thiols will be discussed later, along with oxidation via disulfides to sulfinic esters (Sec. 11.2).

3. THIO ACIDS AND DERIVATIVES

Our introduction at VU to thio acids was through preparation of an invited review,[19] but our actual experimental work began with thio acids as precursors

to carbonyl disulfides, RC(O)SSR'.[21-25] The thio acids needed that were not commercial were prepared usually from acid chlorides and potassium hydrosulfide, a method of Noble and Tarbell;[20] crude yields were 43–80% and purities by KI_3 titration were 72–100%.[21] The thio acids, as their salts, were converted to unsymmetrical carbonyl disulfides by a novel reaction with thiosulfonates (eq. 4);[21-24] a cyclic thiosulfonate (**8**) also could be used (eq. 5).[24] Sulfenyl halides sometimes gave better results, however (eq. 6);[21] for example, the approach of

$$R^1S^- + R^4SO_2SR^5 \longrightarrow R^1SSR^5 + R^4SO_2^- \quad (4)$$

R^1 = Alk C(O);[22] ArC(O);[21,22] R^2R^3NC(S)[23] R^5 = Alk; Ar[22]

$$RC(X)SNa + (CH_2)_4SO_2S \longrightarrow RC(X)SS(CH_2)_4SO_2Na \quad (5)$$

X = O, S **8**

$$R^1SH + R^4SCl \longrightarrow R^1SSR^4 \quad (6)$$

R^1 = Alk C(O);[21] ArC(O);[21] R^2R^3NC(S)[23] R^4 = Alk;[21,23] Ar[21]

eq. 7 was the best of seven explored for the synthesis of various β-substituted ethyl acetyl disulfides.[25] Nevertheless, the fact that a thiosulfonate only monothioalkylated **9** to give **10**, while dimethyl sulfate dialkylated **9** to give **11** (eq. 8),[23] indicates that the relatively

$$AcSCl^{25} + HS(CH_2)_2X \longrightarrow AcSS(CH_2)_2X \quad (7)$$

$$ArSO_2N{=}C(S^-)_2 \longrightarrow ArSO_2N{=}C(SR^1)(SR^2) \quad (8)$$

9

10, R^1 = H; R^2 = S Alk

11, R^1 = R^2 = Me

low electrophilicity and reactivity of thiosulfonates sometimes may afford desirable selectivity. As with the unsymmetrical disulfides of Sec. 5.2.1, the identity of the carbonyl disulfides was checked by spectra;[21,23-25] the absence of

symmetrical disulfides also was assured by TLC[21-25] and occasionally by column chromatography[22,25] and/or GLPC.[21,22] Various structural confirmations were obtained by X-ray[23] and independent synthesis,[21-23,25] as well as by chemical reactions,[22] including disproportionation to the symmetrical disulfides (cf. Sec. 5.2.1).

Adverse biological effects of thioamides, such as enzyme inactivation, tissue damage, and liver toxicity, led us to seek causes in terms of reactive metabolites produced during oxidative desulfurization.[26a] At least 50% incorporation of ^{18}O from oxidation by H_2O_2 in $H_2{}^{18}O$, together with acylation of amines by intermediates, led us to the same conclusions Dyroff and Neal drew from biological studies,[26b] i.e. that a thioamide *S*-oxide forms [i.e. $RC(=SO)NH_2$], followed by conversion to the *S*,*S*-dioxide [i.e. $RC(=SO_2)NH_2$], which then acylates biologically important nucleophiles, such as the ϵ-amino group of lysine.[26b] Conceivably an *S*,*S*,*S*-trioxide and/or a three-membered oxathiirane *S*-oxide also may be involved.[26a]

Concern has developed in recent years as to the extent of mutagenicity and carcinogenicity of thioacetamide.[27] Despite the report of weak carcinogenicity, mutagenicity of thioacetamide was not detected in the standard Ames assay by others or ourselves.[27] It occurred to us that thioacetamide *S*-oxide, however, might be a mutagen and indeed it proved to be mutagenic at high concentrations, consistent with weak carcinogenicity ("weak," nevertheless, suggests that thioacetamide should be handled carefully).[27] A noteworthy chemical aspect was that our melting point of the *S*-oxide in the range of 124–126°C contrasted with two in the range of 134–137°C for the *S*-oxide obtained earlier by others with different methods.[27] Polymorphism explained the difference, but since this explanation could have been a temptingly fallacious effort to force identity on actually different compounds we strained (successfully) to establish polymorphism as a cause, by NMR spectra, elemental analyses, and (especially) identity of IR spectra (KBr) with published values.[27]

Work on a β-thiolactone will be discussed in Sec. 15.1 (cf. eq. 53).

4. MERCAPTALS (THIOACETALS) AND MERCAPTOLES (THIOKETALS)

Although aldehydes and ketones that form stable hydrates give α-hydroxy sulfides with thiols under mild non-acidic conditions and do not proceed to mercaptals or mercaptoles (Sec. 2.2), under various special conditions 2-aminoethanethiol hydrochloride (**12**) could be converted to mercaptals of formaldehyde (**13**) and glyoxylic acid (**14**) and to a ketal of diethyl oxomalonate (**15**; low yield),[28] even though all three of these carbonyl compounds form stable hydrates. As expected, benzaldehyde and acetone under conventional acidic conditions gave a mercaptal (**16**) and mercaptole (**17**), respectively; formic acid gave an orthothioformate (**18**).[28]

$$2\ Cl^-NH_3^+(CH_2)_2SH + RR'CO \rightarrow RR'C(SCH_2CH_2NH_3^+Cl^-)_2 + H_2O$$

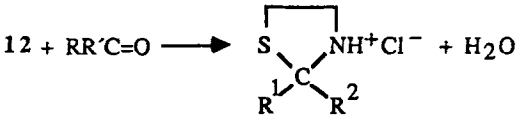
12

13, R = R′ = H **16**, R = H; R′ = Ph

14, R = H; R′ = CO_2H **17**, R = R′ = Me

15, R = R′ = CO_2Et **18**, R = H; R′ = $SCH_2CH_2NH_3^+Cl^-$

It might be added that when several carbonyl compounds simply were heated with **12** in the absence of extraneous acid, thiazolidines resulted (eq. 9); the compounds used were chloral, acetone, phenylglyoxal, and isatin.[28] As before, the idea behind all of this work



(9)

was to learn whether medicinally important thiols could be converted to useful prodrugs; the conclusion, however, was that such structures as **13–18** and thiazolidines were too firmly locked together to afford thiols practicably,[28] unlike the α-hydroxy sulfides mentioned in Sec. 2.2; **15** nevertheless showed significant antiradiation activity (Table 5, Entry 9).

5. DISULFIDES

5.1. *Synthesis*

A review of syntheses (and other aspects) of disulfides seems likely still to be useful.[29] Eq. 10 illustrates a synthesis that has been of special interest to us; a thiosulfonate (**19**) desired for thioalkylating various thiols can be prepared once and then kept indefinitely, but there is some disadvantage of course in that the sulfinic acid fragment (**20**) is lost. The reaction of thiolate salts by eq. 10 is fast and complete even at −86°C.[30] With thiols, on the other hand, reaction is fairly rapid but may proceed only part way; it can be pushed further

$$R^1SO_2SR^2 + {}^-SR^3 \longrightarrow R^1SO_2^- + R^2SSR^3 \qquad (10)$$

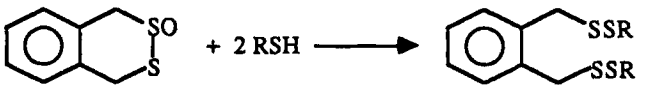
19 **20**

with excess reagents.[30] Eq. 3 gave one illustration of the generality of the thiosulfonate route for a special purpose; there, yields exceeding 50% were obtained with a primary, secondary, or tertiary alkanethiol, an arene- or heterocyclic thiol, or a mercaptoamino acid.[17] Many types of thiols react satisfactorily according to the general application of eq. 10: alkane-,[31–33] arene-,[31,34] and heterocyclic mon-

othiols;[32] alkylene-,[35] arylene-,[7,35] and alkylidenedithiols;[35] and, the various types of thio acids mentioned in Sec. 3;[21-24] similar reactions of cyclic thiosulfonates are discussed in Sec. 5.3.1. Steric hindrances of R^2 often reduce the reactivity of **19** more than do electronic effects,[30] but yields still were good with R^2 = *t*-Bu or 2,4,6-trisopropylphenyl.[30]

Since formation of unsymmetrical disulfides by eq. 10 usually is kinetically controlled while the disproportionation to symmetrical disulfides discussed below usually is thermodynamically controlled, it is prudent to isolate the unsymmetrical products using the mildest conditions and shortest times possible. With aminoalkyl disulfides (which are particularly prone to disproportionate), for example, one procedure was to extract any unchanged thiol, liberate the amino disulfide free base from its hydrochloride product and, after extracting it, quickly reconvert it to the salt.[34,47] Many of our products, however, have been salts that could be conveniently isolated by precipitation with ether from the alcohol used for the synthesis, followed by reprecipitation, with rejection of a first fraction and with leaving of a small amount unprecipitated (cf. refs. 36, 37, and earlier papers in the disulfide series); some disulfides were purified on acid-washed alumina[38] or silica gel,[25,39,41] however, and occasionally even distillation could be used.[25] Some unsymmetrical disulfides were very unstable in solution, but could be kept as solids under Ar in the dark at −80°C.[40] As remarked in Sec. 3, sulfenyl halides sometimes may give better results in disulfide synthesis than thiosulfonates,[21,42] but the reverse also may be true.[33]

Thiosulfinates differ interestingly from thiosulfonates in reactions with thiols in that others have shown that *both* sulfur atoms of thiosulfinates end up as disulfides; our reaction of the cyclic thiosulfinate **21** with a thiol illustrates this point.[39] Other syntheses of disulfides from thiols that we explored include oxidation with lead tetraacetate



21

(eq. 11),[43] reaction with thionitrites (eq. 12),[44] and the elegant route of Brois, Pilot, and Barnum, where all by-products vaporize (eq. 13).[44] Interestingly, lead tetraacetate does not cleave 2-mercaptoethanol, as it does glycols, but simply produces the disulfide; similarly, it first oxidizes a thiol when one is mixed with a glycol.[43]

$$2RSH + Pb(OAc)_4 \longrightarrow RSSR + Pb(OAc)_2 + 2AcOH \quad (11)$$

$$RSNO + R'SH \longrightarrow RSSR' \quad (12)$$

$$RSH + R'SSCOMe \longrightarrow RSSR' + COS + MeOH \quad (13)$$

5.2. *Reactions*

5.2.1. *Disproportionation.* A key issue with unsymmetrical disulfides is the often reversible disproportionation to give the two symmetrical disulfides (eq. 14). In Sec. 3, several means were mentioned for assuring the identity and homogeneity of unsymmetrical carbonyl disulfides; some of these used with other types of disulfides have been independent synthesis,[17] NMR spectra,[21,36,39] and IR spectra (which usually resembled a

$$2RSSR' \rightleftharpoons RSSR + R'SSR' \quad (14)$$

summation of the IR spectra of the symmetrical disulfides but also showed useful gains and losses of bands).[15-17,31] Other means not yet mentioned have included mass spectra,[21,39-41] acid-base properties such as neutralization equivalent,[17] melting behavior,[42] or contrast of one component of eq. 14 in solubility,[15,31,34] or in some other characteristic,[31,37,42,45] For example, in aqueous solutions of aminoethyl aryl disulfide hydrochlorides, as little as 0.5% of the nearly insoluble symmetrical diaryl disulfide could be detected as haziness.[16,34]

Over the years, from time to time, we have studied the disproportionation of a wide variety of disulfides. Comparisons of the results sometimes have been complicated by factors such as differences of analytical method, of solubility, or of temperatures needed to effect reactions in feasible times. However, since all of these results never have been compared before in one place, efforts to show relative ease of disproportionation now are summarized for reactions in H_2O (or D_2O) in Table 1, in alcohols in Table 2, and in other solvents in Table 3. The enormous variations are fascinating, varying in water for example for 50% disproportionation from 0.2 hour at ca. 25 °C to 460 hours at 68 °C (Table 1, Entries 1 and 35 respectively).

The disproportionations of Tables 1–3 were done in the dark except where otherwise stated. "Disproportionation, %" in the tables was based on eq. 14 and calculated as 2(RSSR or R'SSR')(100)/RSSR'. In each table, the relative (decreasing) ease of disproportionation should be fairly reliable for disulfides studied at the same temperature. However, to permit intercalation of other results, so as to afford the (rough) comparisons of Tables 1–3, three assumptions were made: (1) That "For most reactions increasing the temperature only 10 °C will cause the reaction rate to double"[46] (an increase of 21 °C approximated this assumption by increasing the "%" by 4.6–5.4).[34] (2) That times for disproportionation values other than 50% could be converted to times for 50% by a simple proportion. (3) That "trace" or "onset" reported in the references represented ca. 5% disproportionation.

TABLE 1. Disproportionation of Unsymmetrical Disulfides in H_2O (or D_2O)

Entry	For RSSR' R	R'	Temperature, °C	Time, h	Disproportionation, %	Ref.
1	2-[$NaO_2S(CH_2)_4$-$SSCH_2$]$C_6H_4CH_2$	$(CH_2)_4SO_2Na$	ca.25	0.2[a]	50	41
2	4-MeC_6H_4	$CH_2CH(OH)CH$-$(OH)CH_2SO_2Na$	ca.25	0.3[b]	50 (D_2O)	40
3	4-MeC_6H_4;[c] 2,4,6-$(MeO)_3C_6H_2$;[c] $NaO_2S(CH_2)_4SS$-$CH_2CH(OH)CH(OH)CH_2$[a]	$(CH_2)_4SO_2Na$	ca.25	0.4	50 (D_2O)	52 49
4	4-MeC_6H_4; Ph	$(CH_2)_3SO_2Na$	ca.25	0.7	50	52
5	$NaO_2S(CH_2)_4SS(CH_2)_4$	$(CH_2)_4SO_2Na$	68 25	0.05 3	50 (D_2O)[c] 50[a,c]	49 37
6	$AcNH(CH_2)_2$	1-$C_{10}H_6$-8-SO_2Na	ca.25	1.8	50[a,c]	53
7	$NaO_2S(CH_2)_3SS$-$(CH_2)_4$	$(CH_2)_3SO_2Na$	68	0.2	56 (D_2O)	49
8	4-MeO, 4-ClC_6H_4; 3,4-Cl_2,2,6-$Cl_2C_6H_3$	$(CH_2)_4SO_2Na$	ca.25	4	48–54[a,d]	37
9	4-$O_2NC_6H_4$	$(CH_2)_2NH_3^+$	68	0.2	50[e]	34
	4-MeC_6H_4; Ph	$(CH_2)_5SO_2Na$	ca.25	5	50	52
10	$AcNH(CH_2)_2$	$(CH_2)_4SO_2Na$	61	0.7	50[c,e]	33
11	$NaO_2S(CH_2)_5SS$-$(CH_2)_4$	$(CH_2)_5SO_2Na$	68	0.6	50 (D_2O)[c]	49
	4-MeC_6H_4	$(CH_2)_4SO_2Na$	25	9	50 (D_2O)[a,k]	42
12	$H_3\overset{+}{N}(CH_2)_2SS$-(Z)-$(CH_2CH{=}CHCH_2)$	$(CH_2)_2NH_3^+$	68	0.7	50[e] (D_2O)	36
13	4-ClC_6H_4	2-$PhCO_2Na$	ca.25	24	90	48
14	$AcNH(CH_2)_2$	2-biphenylyl-2'-SO_2Na	ca.25	16	36[a,c]	53
15	$HO_2C(CH_2)_2$	$(CH_2)_4SO_2Na$	ca.25	16	30[a,c]	37
	Ph	2-$C_6H_4CO_2H$	ca.25	24	46[f]	48
	4-$MeOC_6H_4CH_2$	$(CH_2)_4SO_2Na$	68	1.7	50[c,e]	42
16	*n*-Bu	2-$C_6H_4CO_2Na$	ca.25	24	40	48

17	4-Me	$(CH_2)_2NH_3^+$ (cf. Entry 30 done in the dark)	ca.25 104	36 3	46[a] 68[a]	31 31
	4-[$H_2N(CH_2)_2SS$]-$(CH_2)_4$	$(CH_2)_2NH_2$ (cf. Entry 29 for the salt)	100	0.4	60–90[a]	35
18	*n*-Bu	$(CH_2)_4SO_2Na$	ca.25	86	50[a,c]	51
19	2,6-$(MeO)_2C_6H_3$	$(CH_2)_2NH_3^+$	68	6	50[c]	16
20	2-ClC_6H_4	$(CH_2)_2NH_3^+$	68	12	50[c]	16
	1-$H_3^+N(CH_2)_2SS$-2-C_6H_4	$(CH_2)_2NH_3^+$	100	3	100[a]	35
21	$HO_2C(CH_2)_2$	$(CH_2)_{3\text{-}5}SO_2Na$	68	1.3	ca.5	52
22	$HO_2CCH_2CH(CO_2H)$; Et; $HO(CH_2)_2$	$(CH_2)_4SO_2Na$	ca.25	168	36–39[a,d]	51
23	1-$H_3^+N(CH_2)_2SS$-4-CH_3-6-C_6H_3	$(CH_2)_2NH_3^+$	100	2	50[a,c]	35
24	4-ClC_6H_4	$(CH_2)_2NH_3^+$	68	19	50[c]	34
25	2- or 4-$C_6H_4CO_2H$	$(CH_2)_2NH_3^+$	100	3	46–51[a]	15
	2-$NO_2C_6H_4$	$(CH_2)_2NH_3^+$	68	23	50[c]	16
26	2-$MeOC_6H_4$	$(CH_2)_2NH_3^+$	68	42	50[c]	16
27	2-MeC_6H_4	$(CH_2)_2NH_3^+$	68	60	51	16
	Ph	$(CH_2)_2NH_3^+$	68	60	50[g]	34
	$H_3^+N(CH_2)_2SS$-(E)-$(CH_2CH=CHCH_2)$	$(CH_2)_2NH_3^+$	68	62	50[c] (D_2O)	36
28	3-$HO_2CC_6H_4$	$(CH_2)_2NH_3^+$	100	10	50[a,c]	15
	$HO_2CCH(NH)_2CMe_2$	$(CH_2)_4SO_2Na$	100	1	trace (5)	44
29	2[$H_3^+N(CH_2)_2SS$]-$(CH_2)_2$	$(CH_2)_2NH_3^+$	100	13	50[a,c]	35
	2-$HOCH_2C_6H_4$	$(CH_2)_2NH_3^+$	68	105	50[c]	16
	4-[$H_3^+N(CH_2)_2SS$]-$(CH_2)_4$	$(CH_2)_2NH_3^+$	100	14	50[a,c]	35
30	4-Me, 4-$MeOC_6H_4$; 2,4,6-$(i\text{-}Pr)_3C_6H_2$	$(CH_2)_2NH_3^+$	68	120–138[c,d]	50	34
31	3-$O_2CC_6H_4$; 2-$MeO_2CC_6H_4$	$(CH_2)_2NH_3^+$	100	22	45–51[a,d]	15
32	*t*-Bu	$(CH_2)_4SO_2Na$	ca.25	168	2[a]	51
33	$HO_2CCH(NH_2)CMe_2$	$(CH_2)_2NH_3^+$	100	4	trace (5)	44

(*Continued*)

TABLE 1. Disproportionation of Unsymmetrical Disulfides in H_2O (or D_2O) (*Continued*)

Entry	For RSSR′ R	R′	Temperature, °C	Time, h	Disproportionation, %	Ref.
34	$PhCH_2S(O)_2(CH_2)_4$	$(CH_2)_2NH_3^+$	100	72	79	54
			61	8	trace (5)	33
	$2\text{-}O_2CC_6H_4$[h]	$(CH_2)_2NH_3^+$	100	22	21–24[a,d,i]	15
35	$2[H_3\overset{+}{N}(CH_2)_2SSCH_2]\text{-}C_6H_4CH_2$	$(CH_2)_2NH_3^+$	68	460	50[e] (D_2O)	36
	HO_2CCH_2; $NaO_3S(CH_2)_4$	$(CH_2)_2NHAc$	61	ca.96	trace (5)	33
36	$2\text{-}O_3SC_6H_4$	$(CH_2)_2NH_3^+$	100	168	59	16
			68	60	28	16
37	$HO_2C(CH_2)_{2\text{-}4}$	$(CH_2)_2NHAc$	61	ca.384	trace (5)	33
	$HO_2CCH(NH_2)CMe_2$	$(CH_2)_2NHAc$	100	24	trace (5)	44
	$4\text{-}O_2CC_6H_4$	$(CH_2)_2NH_3^+$	100	22	4[a]	15
38	$PhCH_2$	$CMe_2CH(NHAc)\text{-}CO_2H$	100	40	trace (5)	44
39	$4\text{-}MeC_6H_4CH_2$	$(CH_2)_2\overset{+}{N}H_2\text{-}n\text{-}Dec$	100	480	35	48
40	*t*-Bu	$(CH_2)_2NH_3^+$	104	20	0[a,j]	31

[a]Under ambient light, which undoubtedly accelerated the disproportionation.
[b]For the *threo* form; for the *erythro* form, ca. 0.8 h.
[c]From a plot of results at more than one time.
[d]Range for the compounds shown.
[e]Apparently the equilibrium value.
[f]At pH 7.6; disproportionation varies greatly with pH (e.g., 24 h leads to 70% at pH 8.5 but only 13% at pH 6.4).
[g]Other results are 47% in 60 h at 68°[16] and 80%[48]–81%[34] in 160 h at 68° [the result of 45% in 25 h at 68 °C (ref. 16) is out of line and evidently wrong].
[h]Two different crystalline forms.
[i]At 25 °C, 24 h led only to ca. 1% disproportionation (dark).[48]
[j]Since the disulfide of Entry 40 was not carried beyond 20 h, no conclusion can be drawn as to relative order.
[k]This result, obtained in D_2O by NMR, seems less reliable than that of Entry 3, done in H_2O by several isolations.

TABLE 2. Disproportionation of Unsymmetrical Disulfides in EtOH or MeOH

Entry	For RSSR′ R	R′	Solvent[a]	Temperature, °C	Time, h	Disproportionation, %	Ref.
1	$NaO_2SCH_2CH(OH)CH(OH)CH_2SS$-$CH_2CH(OH)CH(OH)CH_2$	$CH_2CH(OH)CH(OH)CH_2SO_2Na$	d_4-M	ca.25	0.4–1.9[b]	50[h]	40
2	$AcNH(CH_2)_2$	1-$C_{10}H_6$-8-SO_2Na	M	50	0.1	33[c,d]	45
3	2-$[NaO_2S(CH_2)_4SSCH_2]C_6H_4CH_2$	$(CH_2)_4SO_2Na$	d_4-M	ca.25	13	50[d,h]	41
4	$AcNH(CH_2)_2$	$(CH_2)_4SO_2Na$	M	61	8	50–55[e]	33, 50
5	2-$[HOCH_2CH(OH)CH_2SSCH_2]$-$C_6H_4CH_2$	$CH_2CH(OH)CH_2OH$	M	ca.25	8–9	trace (5)[d]	39, 41
6	1-[$AcNH(CH_2)_2SS$]-1-cyclohexyl	$(CH_2)_2NHAc$	E	100	0.7	50[d,h]	35
	4-MeC_6H_4	$(CH_2)_4SO_2Na$	M	65	0.8	trace (5)	42
	2-[4-Me-$C_6H_4SSCH_2]C_6H_4CH_2$	4-MeC_6H_4	M	ca.25	10–12	trace (5)[d]	39, 41
7	4-MeC_6H_4	$CH_2CH(OH)CH(OH)$-CH_2SO_2Na	d_4-M	ca.25	7	ca.2[f]	40
8	4-MeC_6H_4	(S)CNH_2	E	100	3	100[g]	23
9	4-MeC_6H_4	(S)$CNMe_2$	E	100	3	47	23
10	$AcNH(CH_2)_2$	(S)$CNMe_2$	E	100	3	30	23
11	4-$NCC_6H_4CH_2$	$(CH_2)_2NH_2^+$-*n*-$C_{10}H_{21}$	E	100	8	50[h]	47
	4-$[H_3^+N(CH_2)_2SS](CH_2)_4$	$(CH_2)_2NH_3^+$	E	100	3	19–35[d,i]	35
12	4-$O_2NC_6H_4CH_2$	$(CH_2)_2NH_2^+$-*n*$C_{10}H_{21}$	E	100	13	50[h]	47
13	4-MeC_6H_4	(S)CC_6H_4-OMe-4	M	68	19	trace (5)	42
14	4-MeC_6H_4	$(CH_2)_2NHAc$	E	100	48	50[d,h]	15
	3-$O_2NC_6H_4CH_2$	$(CH_2)_2NH_2^+$-*n*-$C_{10}H_{21}$	E	100	40	50[h]	47
	2-[$AcNH(CH_2)_2SS](CH_2)_2$	$(CH_2)_2NHAc$	AE	100	40	50[d,h]	35
15	3-$NCC_6H_4CH_2$	$(CH_2)_2NH_2^+$-*n*-$C_{10}H_{21}$	E	100	71	50[h]	47
16	2-$AcNH(CH_2)_2$	2-$C_6H_4CO_2H$	E	100	125	50[d,h]	15

(*Continued*)

TABLE 2. Disproportionation of Unsymmetrical Disulfides in EtOH or MeOH (*Continued*)

Entry	For RSSR′ R	R′	Solvent[a]	Temperature, °C	Time, h	Disproportionation, %	Ref.
17	4-$ClC_6H_4CH_2$	$(CH_2)_2NH_2^+$-*n*-$C_{10}H_{21}$	E	100	170	50[h]	47
	$AcNH(CH_2)_2$	$(CH_2)_2NH_2^+$-*n*-$C_{10}H_{21}$	E	100	72	22	38
	4-[$AcNH(CH_2)_2SS$]$(CH_2)_4$	$(CH)_2NHAc$	AE	100	72	>20[d]	35
18	$AcNH(CH_2)_3$	$(CH_2)_2NH_2^+$-*n*-$C_{10}H_{21}$	E	100	72	13	38
	t-Bu	$(S)CNMe_2$	E	100	72	13	23
19	$PhCH_2$	$(CH_2)_2NH_2^+$-*n*-$C_{10}H_{21}$	E	100	390	50[h]	47
20	4-Me, 4-$MeOC_6H_4CH_2$	$(CH_2)_2NH_2^+$-*n*-$C_{10}H_{21}$	E	100	530	50[h]	47
21	Ph	2-$C_6H_4CO_2H$	E	ca.25	24	0[j]	17
	4-$MeC_6H_4SSCH_2CH(OH)CH(OH)CH_2$	4-MeC_6H_4	M	ca.25	48	0[d,j,k]	39
	4-[$HOCH_2CH(OH)CH_2SS$]-$CH_2CH(OH)CH(OH)CH_2$	$CH_2CH(OH)CH_2OH$	M	ca.25	48	0[d,j,k]	39
	$PhCH_2S(O)_2(CH_2)_4$	$(CH_2)_2NHAc$	M	61	8	0[j]	33, 50
	$PhCH_2S(O)_2(CH_2)_4$	$(CH_2)_2NH_3^+$	M	61	8	0[j]	33, 50
	1-[$AcNH(CH_2)_2SS$]-1-cyclopentyl	$(CH_2)_2NHAc$	E	100	3	0[d,j]	35

[a]AE, 100% EtOH; E, 95% EtOH; M, MeOH; d_4-M, CD_3OD.

[b]The 2,3-dihydroxybutyl groups represent several combinations of *threo* and *erythro* forms. These disulfides disproportionated so rapidly in D_2O that they could not be studied in D_2O at ca.25 °C.

[c]The 33% is the yield of the disulfide dioxide formed by cyclization (see ref. 45).

[d]Under ambient light, which probably accelerated the disproportionation.

[e]Apparently an equilibrium value.

[f]For the *erythro* form; for the *threo*, ca. 4%; cf. Entry 2 in Table 1.

[g]Decomposed (100%) to $(p\text{-}MeC_6H_4S)_2S$; see ref. 23 for details.

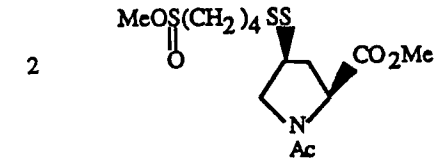
[h]From a plot of results at more than one time.

[i]In 1 M HCl, 75–90%.

[j]Since the disulfides of Entry 21 were not carried beyond the times shown, no conclucions can be drawn as to relative order.

[k]Both diastereomers were comparable.

TABLE 3. Disproportionation of Unsymmetrical Disulfides in Other Solvents

Entry	For RSSR′ R	R′	Solvent[a]	Temperature, °C	Time, h	Disproportionation, %	Ref.
1	C_6Cl_5	(S)CN$(CH_2CH_2)_2$O	B	25	0.3	trace (5)[b]	42
2			EA	77	7	trace (5)[c,d]	55
3	$CH_3C(O)$	Ph	D	100	65	50[e]	22
	p-MeC_6H_4	(S)$CNMe_2$	D	100	24	16	23
	$CH_3C(O)$	$(CH_2)_2$NHAc	D	100	82	50[e]	22
4	PhC(O)	$(CH_2)_2$NHAc	D	100	159	50[e]	22
5	AcNH-$(CH_2)_2$	(S)$CNMe_2$	D	100	24	4	23
6	t-Bu	(S)$CNMe_2$	D	100	72	3	23
7	Me	(O)CMe	D	100	1872	50[e,f]	21
8	Me	(O)C-t-Bu	D	100	1872	16[f]	21
9	Ph	2-$C_6H_4CO_2H$	D	100	24	<3[g]	17
			A	100	119	<2[g]	17
	Ph	(O)CPh	D	100	48	0	22

[a] A, glacial acetic acid; B, benzene; D, 1,4-dioxane; EA, ethyl acetate.

[b] Equilibrium appeared to exist after 1 h (no further change). Even the solid disproportionated significantly after a week at 5 °C.

[c] Under ambient light, which probably accelerated the disproportionation.

[d] In contrast to the diester, the disodium salt began to disproportionate in ca. 15 min (in MeOH). The 4-diastereomer of the diester (disulfide moiety below the ring plane) began to disproportionate in 1.5 h in refluxing EA.

[e] From a plot of results at more than one temperature.

[f] Since reactions other than disproportionation also occur, % refers to the total loss. Under UV irradiation at 25 °C in dioxane, 50% of MeSS(O)CMe was lost in 528 h but reversal of relative stabilities led to 50% loss of MeSS(O)C-t-Bu after only 240 h.

[g] Since the disulfides of Entry 9 were not carried beyond the times shown, no conclusions can be drawn as to relative order.

In each table, horizontal rules divide the disulfides into five groups, roughly in order of decreasing ease of thermally induced disproportionation; members of each group are similarly ordered, but the differences among them are less striking. Disulfides in the last group of each table were not observed long enough to permit comparisons. "Ties" are given the same entry number. The references cited in Tables 1–3 also report many results of photochemically induced disproportionation, but attention cannot be given to those details here.

Among the more important conclusions from our studies of disproportionation are the following:

(1) Good evidence was developed that disproportionation can be induced either thermally in the dark *or* photochemically, proceeding respectively by heterolytic or homolytic mechanisms.[34] The heterolytic mode can be understood as generation of thiolate ions, which then attack the unsymmetrical disulfide in chain-type processes (cf. refs. 33, 47), and the homolytic mode by similar chain-type processes but involving thiyl free radicals. Protection from light as well as heat thus is a wise precaution; for example, compare Table 1, Entries 17 (ambient light) and 30 (dark) for *p*-$MeC_6H_4SS(CH_2)_2NH_3Cl$; actual UV irradiation led to 98% disproportionation in 45 min at ca. 25 °C;[31] (cf. also Table II of ref. 34 regarding effects of light).

(2) The thermally induced heterolytic reaction showed first-order dependence on the unsymmetrical disulfide.[34,47] The rate was unaffected by a ten-fold dilution,[33,47–49] and it showed a positive salt effect.[34] There was good correlation with Hammett σ constants, and since ρ = 1.1–1.9, electronegative substituents such as *p*-nitro markedly accelerated the thermal reaction.[34,47] Acclceration also occurred with addition of alkalis, thiols, or strong acid (where sulfenium ions, RS^+, may be involved).[34]

(3) In contrast, in UV-induced homolysis the order of substituent effects was virtually inverted; consequently even though a *p*-nitroaryl disulfide was one of the least stable thermally, the stabilizing effect of the nitro group toward light made the *p*-nitro compound actually easier to purify;[34] this effect also seemed true of the *o*-nitro isomer, even though the order of *ortho* substituent effects is unpredictable.[16] Acrylamide was polymerized when added to a light-induced reaction, consistent with homolysis, but not when added to a thermally induced reaction in the dark.[34]

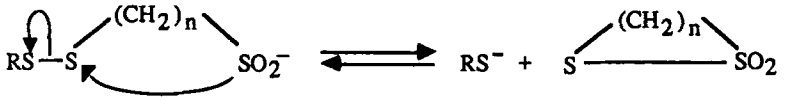
(4) As eq. 14 indicates, the disproportionation ordinarily is reversible,[33,50] and footnotes to Tables 1–3 point to several instances of equilibria. In many instances, however, separation of a nearly insoluble product,[34] or other ill-understood considerations,[47] can force the disproportionation virtually to completion.

(5) Not surprisingly, unsymmetrical disulfides are far more stable as solids than in solution.[15,31,33,50] Nevertheless, disproportionation *can* occur,[42] and some unsymmetrical disulfides are unstable as solids, even in the dark under N_2.[24]

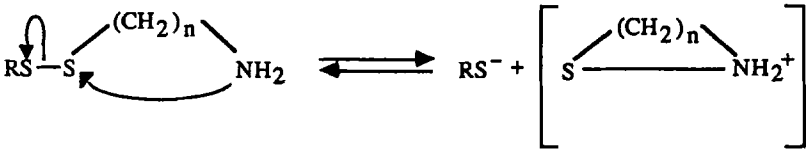
(6) Examples in Tables 1–3 show that these disulfides ordinarily disproportionate much more rapidly in water than in alcohols and in alcohols more rapidly than in inert solvents; with salts such as those containing $-SO_2Na$, this effect may reflect increased ion pairing in nonaqueous solvents (and thus less neighboring group effect of the kind discussed below).[33] Thus one can compare the following results in different solvents: Entries 15 of Table 1, 21 of Table 2, and 9 of Table 3; Entries 2 of Table 1 and 7 of Table 2; and, Entries 10 of Table 1 and 4 of Table 2; indeed, Entry 1 of Table 2 states that rapid reaction actually precluded study in D_2O (see also refs. 23 and 49).

(7) In the thermally induced disproportionations, neighboring group effects can be quite important (we never got around to exploring such effects much in photochemical reactions). With disulfides containing amino groups, the tendency toward disproportionation decreases in the following order (numbers are for illustrative entries in Table 1): amines (17) > HCl salts (29) > zwitterions (25 vs. 34, 37) > amides (33 vs. 37) (see also refs. 31, 34, 44, 47); indeed, disulfides with free NH_2 groups typically are quite unstable because of rapid disproportionation.[34,36,47] Where carboxyl groups are involved, the order is acid (25) > ester (31),[15] and where $-SO_2H$ groups are involved, the order is sulfinate salt (10) > the corresponding sulfone (34) or sulfonic acid salt (35).[33]

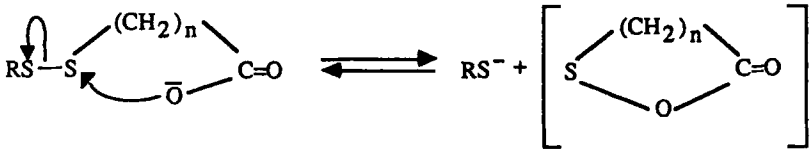
We have attributed effects of these kinds in (7) principally to unusually facile generation of initiating thiolate ions through neighboring group interactions of the kind illustrated in eqs. 15–17. The thiolate species thus generated then attack the unsymmetrical disulfide,



22 (15)



(16)



(17)

followed by chain-type continuations as mentioned above. Some further points of evidence for such neighboring group involvements in disproportionation are the following:

(a) The relative accelerating effectiveness of the functional groups mentioned above within each series of amines, carboxylic acids, and sulfinic acids are in the order of their expected relative nucleophilicities.

(b) With eq. 15, when RS^- was trapped, the stable dioxide **22** could be isolated in 39% yield.[33] Other dioxides were isolated later even without traps, for example with Entries 6 and 14 of Table 1 (where the % is for the dioxide; see also refs. 37 and 51); the cyclization of the naphthyl compound of Entry 6 to the dioxide is faster than that of the biphenyl compound of Entry 14 because of the enforced coplanarity of SS and SO_2^-. Ease of ring formation also explains the relative ease of cyclization of the 4-MeC_6H_4 compounds in Entries 3, 4, and 9 of Table 1, where n of eq. 15 = $4 \geqslant 3 >> 5$; acceleration by other such cyclizations also was encountered.[44] A final point, as mentioned, is that a sulfinate-salt group ($-SO_2^-$; Entry 10) accelerated disproportionation far more than does a less nucleophilic sulfone ($-SO_2R$; Entry 34), or sulfonate ($-SO_3^-$; Entry 35).[33]

(c) With eq. 16, disproportionations of the amino disulfides are first order,[34,47] and the rate does not vary significantly with ten-fold dilution.[47] Even an acetamidoethyl disulfide (Entry 3, Table 3) disproportionates far more rapidly than do simple alkyl disulfides (Entries 7 and 8, Table 3).

(d) With eq. 17, for carboxy disulfides, a benzo counterpart of the unstable bracketed product was characterized (it polymerized in 0.5 h).[48] As one would expect from relative nucleophilicites, the ease of disproportionation decreases in the order mentioned of salts > acids[33,48] > esters.[15] As with eq. 16, dilution had little effect on the rate.[48] Salts with n of eq. 17 = 1 disproportionated faster than with n = 2-4.[33] As one would expect, the effect of $-CO_2^-$ is less than of $-NH_2$.[25]

Tables 1–3 show in a general way the relative effects of the three groups. Thus in Table 1 the most reactive disulfides in the first group are sulfinates. The second group contains some amino disulfides, which then dominate the third and fourth groups. The lower position of carboxy disulfides is illustrated by Entries 13, 15, and 16 of Table 1 and the last groups of Tables 2 and 3. Other groups tried had relatively minor or no effect.[25]

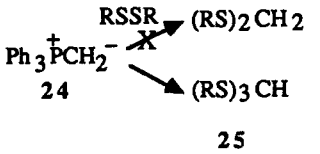
The most reactive disulfide seems to be Entry 1 of Table 3, which began to disproportionate in 0.3 h at ca 25 °C and reached equilibrium in an hour, even in benzene;[42] the reason presumably is that both groups are good leaving groups.

5.2.2. *Insertion reactions.* The possibility that a disulfide might react as a combination of RS^+ and RS^- led us to try inserting carbene-like species into the SS bond.[56] Results were unpromising with dichlorocarbene or a nitrene, but the carbenoidal Simmons-Smith reagent **23** did indeed insert CH_2 into aryl disulfides (eq. 18), even though not into alkyl aryl or

$$CH_2I_2 \xrightarrow{Zn\text{-}Cu} [ICH_2ZnI,\text{-}CH_2:] \xrightarrow{(ArS)_2} (ArS)_2CH_2 \qquad (18)$$

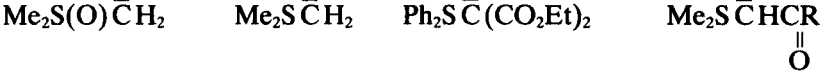
23

dialkyl disulfides; carbenoids from diazo esters inserted similarly (with BF_3 catalysis).[56] A phosphonium ylide (**24**) gave only traces of insertion, the interesting major product being **25** (64% yield; Scheme 4).[56] With aryl disulfides, the sulfur ylide **26** inserted CH_2 to



Scheme 4

account for up to 22% of the products, but reaction of both **26** and **27** with PhSSPh nevertheless led mostly to PhSMe and $(PhS)_3CH$.[57] With catalysis by $BF_3{\cdot}Et_2O$, **28**



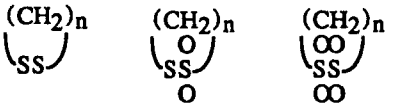
26 **27** **28** **29**

inserted $C(CO_2Et)_2$ into PhSSPh in 26% yield by isolation and in up to 70% yield by NMR, but ylides of structure **29** were only thioalkylated to give $Me_2SCSRC(O)R$.[57] The reader may enjoy comparing explanations for the various reactions with those we offered.[56,57]

5.2.3. *Oxidation.* Oxidation of cyclic disulfides will be discussed next (Sec. 5.3.1), oxidation to sulfinic-acid derivatives in Sec. 11, and oxidation to thiosulfonates in Sec. 13.4.1.

5.3. *Special Types, and Other Aspects*

5.3.1. *Cyclic disulfides.* Syntheses were compared for 1,2-dithiolane (**30**, n = 3), 1,2-dithiane (**30**, n = 4), and 1,2-dithiepane (**30**, n = 5), as well as for the 1,1-dioxides (**31**) and 1,1,2,2-tetroxides (**32**) with n = 3–5;[58] surprisingly, of the six oxides only one was known (**31**, n = 4).[58] The best preparations for the disulfides from the α,ω-dithiols were these: for **30**, n = 3, oxidation at 75 °C (sic!) or depolymerization of the polymer at 80 °C;

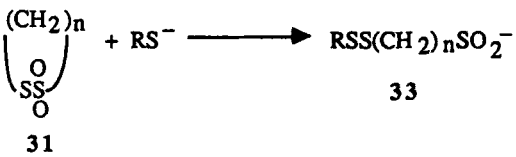


30 **31** **32**

for **30**, $n = 4$, cyclization of the monothiotosylate with alkali or of the lead dithiolate with sulfur; and, for **30**, $n = 5$, an oxidation of the dithiol according to Schöberl and Gräfje with $FeCl_3$.[58] The five- and six-membered disulfides (**30**, $n = 3$ and 4) were best oxidized to the dioxides (**31**) with H_2O_2 in acetic acid,[52, 58] but $NaBO_3$ seemed best for the seven-membered disulfide (**30**, $n = 5$).[52] The six-membered disulfide (**30**, $n = 4$) could be oxidized directly to the tetroxide (**32**, $n = 4$), but the five- and seven-membered tetroxides (**32**, $n = 3$ and 5) had to be obtained from the dioxide; the best approach to the tetroxides was with H_2O_2 in acetic acid, with tungstic acid catalysis.[58] Catalysts were desirable or even necessary in several of these oxidations;[58] for example, H_2O_2 with tungstic acid worked in one instance where many other oxidants did not.[40] An interesting puzzle, for which we must leave the answer to others, is why neither an acyclic alkyl disulfide nor dioxide could be oxidized practicably to the tetroxide.[58]

1,2-Dithiane (**30**, $n = 4$) is somewhat subject to capricious polymerization, but 1,2-dithiolane (**30**, $n = 3$) is extremely so (especially in light) and can be kept for long only in solution in the dark.[58] All of the dioxides (**31**) and tetroxides (**32**) are reasonably stable, however.[58] The UV maxima of the dioxides occur at progressively shorter wavelengths as the size of the ring increases, as with the disulfides, perhaps in part because of decreased ring strain.[58] Hydrolysis, polarographic reduction, and other characteristics were compared for the nine compounds of structures **30–32**, $n = 3$–5.[54]

We hope that the synthetic possibilities illustrated with these prototypes will be useful for many ring-size and ring-substitution situations. An example is the use of the dioxides illustrated by eq. 19; most of the sulfinates of Tables 1–3 were obtained in this way. The sulfinate salts then could be converted to other compounds such as the sulfone

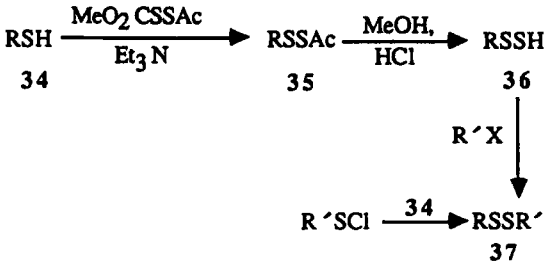


31 33 (19)

(Entry 34) or sulfonate (Entry 35) of Table 1,[54] or the sulfinic ester of Table 3 (Entry 2).[55] Various syntheses also were explored with substituted 1,2-dithiolanes and 1,2-dithianes and their monoxides and dioxides,[59] but we could not obtain a 1,2-dithiane monoxide or dioxide containing a double bond.[41] Some other cyclic disulfides and their derivatives are discussed in Sec. 15.

5.3.2. *Hydrodisulfides.* The biological significance of hydrodisulfides related to cysteine led us to interest in synthesizing models based on an amino acid and stable enough for study.[60] The unprecedented stability of a sulfenyl iodide and thionitrite (Secs. 7.1 and 7.2) based on penicillamine (**5**) drew us to the similarly structured hydrodisulfide **36** as a target (Scheme 5).[60] After several false starts,

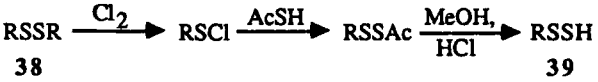
the synthesis of Scheme 5 gave **36** (the key reaction to give **35** was based on eq. 13).[60] The structure of **36** was confirmed by



Scheme 5. R = MeO_2 CCH(NHAc)CMe_2.

spectra, titration with I_2, and conversion to **37**, which was independently synthesized (Scheme 5).[60] Neat **36** decomposed in a few hours, but a solution could be kept for six days and even heated at 55 °C for another day (but washing with aqueous bicarbonate caused immediate loss).[60] The atypical stabilities of **36**, the sulfenyl iodide, and the thionitrite are attributable to steric hindrance like that of similarly structured neopentyl halides (cf. ref. 61).

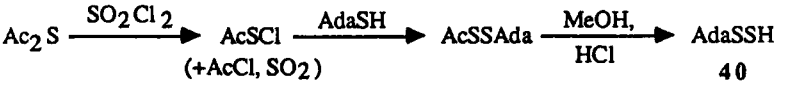
With reason to believe that the stability of **36** might be enhanced by replacing the *N*-acetyl by *N*-tosyl, **39** was sought; **39** could not be obtained by the approach of Scheme 5 because the disulfide **38** withstood all practicable efforts to reduce it to the thiol.[62] The sequence of Scheme 6 succeeded, however, and the structure of **39** was established in the



Scheme 6. R = MeO_2 CCH(NHSO_2 C_6H_4-*p*-Me)CMe_2.

manner of **36**.[62] The neat hydrodisulfide **39** was indeed more stable than **36**, although even it underwent 15% decomposition in 24 h at ca 25 °C.[62]

Another reason for interest in stable hydrodisulfides was possible use of the corresponding thiol as a trap for atomic sulfur (cf. Secs. 9.1 and 17) to give the hydrodisulfide. A nicely stable hydrosulfide (**40**) ultimately was obtained as shown by Scheme 7; the structure was confirmed as with **36** and **39**.[63] To our delight, neat **40** not only could be



Scheme 7. Ada = 1-adamantyl.

analyzed for the elements but could be distilled and kept (sealed) under ambient conditions for more than four months without change.[63]

5.3.3. *Mercaptoalkyl disulfides and sulfinylalkyl disulfides.* Mercaptoalkyl disulfides promised to be an intriguing species, since although the —SH and —SS— functions should undergo thiol-disulfide interchange, the species conceivably might be studied at low temperature, or under acidic conditions to suppress reactivity of SH. Nevertheless, our synthetic attacks on the species were unavailing;[64] perhaps a reader will respond to the challenge.

On the other hand, the incompatible functions of —SH and —S(O)— could be incorporated in one molecule; a redox reaction soon resulted that led to disulfides containing sulfinyl, along with —S— moieties, as will be discussed in Sec. 10.[65,66] Sulfinylalkyl disulfides (**41**), a novel class, could be obtained practicably by the reaction of eq. 20 at −70 °C, although usual conditions led only to the two symmetrical disulfides

$$PhCH_2S(O)(CH_2)_2SSO_2Ar \xrightarrow{RS^-,\ -70°C} PhCH_2S(O)(CH_2)_2SSR + ArSO_2^- \qquad (20)$$

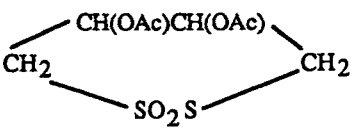
41

possible from **41**.[66] The disulfides **41** were about equally stable in ambient light and in the dark, the first change being noted with R = 4-ClC_6H_4 after ca. 19 h and with 4-CH_3-C_6H_4 after ca. 57 h [this order was attributed to a neighboring group effect of —S(O)—]; under UV irradiation, however, change began in only 7–18 min (respectively).[66] In Sec. 6, the unexpected formation of a sulfinyl disulfide from the trisulfide will be discussed.

5.3.4. *Other aspects.* **Steric hindrance** seemed to play more of a role in the oxidation of disulfides than in their formation from thiols or their spectra.[67,68] Thus the common method of oxidizing disulfides with Cl_2 failed with bis[2,4,6-triisopropylphenyl] disulfide, and H_2O_2 gave only the *S*-monoxide (thiosulfinate), even with WO_3 as a catalyst; the atypical stability of this monoxide (i.e. no change after two years at ca. 25 °C) is consistent with steric resistance to further oxidation.[67] Ultimately, H_2O_2 in AcOH-dioxane with WO_3 *and* conc. HCl with the disulfide did give the *S*,*S*-dioxide **42** (a thiosulfonate) in good yield.[67] On the other hand, there seemed to be nothing particularly unusual in the oxidation of 2,4,6-triisopropylbenzenethiol to the disulfide with iodine or in the UV spectrum of the disulfide.[68] Similarly, the facile oxidation of 4,5-diacetoxy-1,2-dithiane to the monoxide (again, surprisingly stable) but not to the dioxide (**43**) seems likely to be a result of steric hindrance.[59]

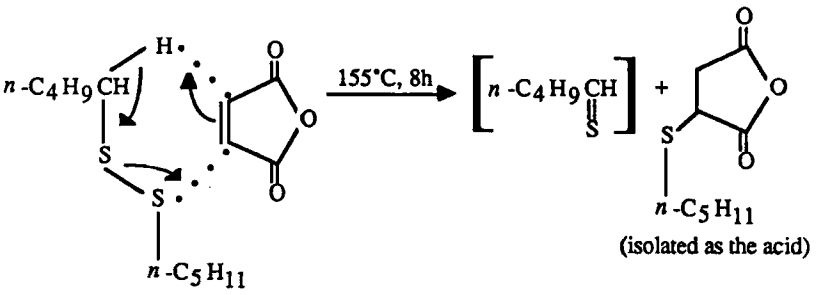
2,4,6-(*iso*Pr)$_3$$C_6H_2SO_2$ SC_6H_2-2,4,6-(*iso*Pr)$_3$

42



43

The **ene reaction** seemed to have a sulfur counterpart in eq. 21, which was uncovered in a study of uncatalyzed reactions of disulfides with double bonds.[69]



(21)

The synthesis and characterization of **carbonyl** and **thiocarbamyl disulfides** were discussed in Sec. 3, and the disproportionations of some of these, as well as of a **thiocarbonyl disulfide** (Table 2, Entry 13), are summarized in Tables 2 and 3.

6. TRISULFIDES AND POLYSULFIDES

A review of some years ago still will afford useful references.[29] One of the preparations for disulfides described there, and in Sec. 5.1 (eq. 10), with substitution of S^{2-} for RS^- provides a nice route to symmetrical trisulfides by dialkylation of the S^{2-}; this route was superior to several others tried (eq. 22).[70] Unfortunately, efforts to make unsymmetrical trisulfides in this way by using two thiosulfonates gave only mixtures,[70] and simple attractive syntheses still

$$2\,RSO_2SR + Na_2S \longrightarrow 2\,RSO_2Na + RSSSR \qquad (22)$$

(R=1° or 3° Alk, or Ar)

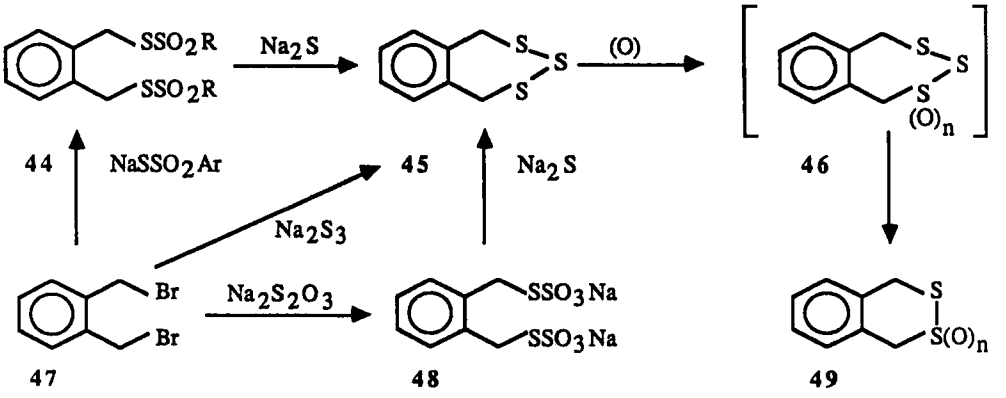
are desirable (cf. ref. 29, p. 331). The IR spectra of the trisulfides differ from those of corresponding disulfides in the region of 250–700 cm^{-1} but not much in that of 700–4000 cm^{-1}.[70]

The research of Scheme 8 opened up the possibility of preparing trisulfides with up to four other functions present; although R in the illustration carries two chloroalkyl groups, R should be subject to wide variation.[71] The bisthiosulfonate **44** also could be

$$ROH \longrightarrow ROSO_2R' \xrightarrow{ArSO_2SNa} RSSO_2Ar \xrightarrow{0.5\,Na_2S} RSSSR$$

Scheme 8. $R = [Cl(CH_2)_3]_2CHCH_2$.

used to synthesize trisulfides (Scheme 9), although the product (**45**) was obtained better from the Bunte salt (**48**, 73% yield) than from **44** (57% yield) or the dibromo compound



Scheme 9

(**47**, 11% yield).[41] Interestingly, although the seven-membered monoxide **46**, $n = 1$ could be obtained, efforts to get the dioxide (**46**, $n = 2$) led only to loss of sulfur and formation of the six-membered disulfide oxides (**49**, $n = 1$ or 2).[41] Numerous attempts to prepare the nonbenzenoid counterpart of **45** (i.e. with only one double band in the 5-position) by ourselves and others were unpromising,[41] thus leaving another challenge for our successors. In reactions like those of eq. 22, cyclic thiosulfonates with Na_2S_x, $x = 1$, yielded trisulfide bissulfinates (Eq. 23, $m = 3$); most of these products were highly hygroscopic and readily gave stable hydrates.[45,50,52]

$$2\ \left(\begin{matrix}(CH_2)_n\\ SO\\ 2\end{matrix}\ \begin{matrix}\\ S\end{matrix}\right) \xrightarrow{Na_2S_x} NaO_2S(CH_2)_nS_m(CH_2)_nSO_2Na \qquad (23)$$

50 **51**

Problems were encountered in the effort to secure sulfinyl trisulfides such as **53** (eq. 24).[66] Thus in eq. 24 Na_2S captured sulfur from the trisulfide **53**, leaving the

$$2\ RS(O)(CH_2)_2SSO_2Ar \xrightarrow{Na_2S,\ H_2O} [RS(O)(CH_2)_2S]_2S \xrightarrow{-S} [RS(O)(CH_2)_2S]_2 \qquad (24)$$

52 **53** **54**

disulfide **54**;[66] extraction of **53** into CH_2Cl_2 as it formed, however, obviated this effect of aqueous Na_2S and led to the trisulfide **53** in 69% yield.[66]

An effort was made to determine the maximum value of m possible in **51** by

varying x (the number of sulfur atoms) of the sodium polysulfide in eq. 23.[72] The highest value of x for Na_2S_x obtainable under our conditions was 6.4. When x of Na_2S_x exceeded 4, however, sulfur precipitated during the reaction with **50**; the product (**51**) then seemed to have m about 5, which was about the value also when x of Na_2S_x was 4.[72] In H_2O, products with $m > 4$ slowly lost sulfur, so that the tetrasulfide appeared to be the maximum sulfinate polysulfide stable for more than a few hours in H_2O (i.e. **51** where $n = 4$, $m = 4$).[72] Later (eq. 23),[52] in a study of variations of n (the number of CH_2 groups), to our astonishment we found that a tetramethylene trisulfide (**51**, with $n = 4$, $m = 3$) in D_2O rearranged completely in the dark at 68 °C in 80 min to give **55** (eq. 25), the sulfur in the polysulfide chain being acquired by a sulfinate function.[52] Consistent with the

$$NaO_2S(CH_2)_4SSS(CH_2)_4SO_2Na \xrightarrow{H_2O,\,\Delta} NaO_2S(CH_2)_4SS(CH_2)_4SO_2SNa \quad (25)$$

(**51**, with **n** = 4, **m** = 4-5) **55**

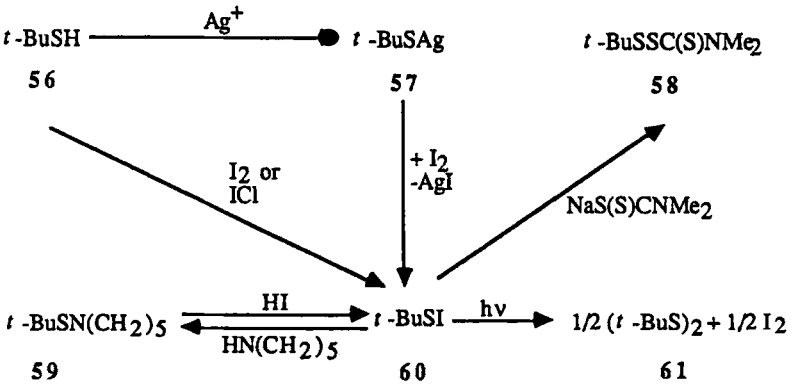
mechanistic involvement of a neighboring group effect of $—SO_2^-$ on —SSS—,[52] of the kind discussed in Sec. 5.2.1, the trimethylene trisulfide (**51**, $n = 3$, $m = 3$) rearranged completely in the dark at 68 °C in 40 min but the pentamethylene trisulfide (**51**, $n = 5$, $m = 3$) only after 18 h. Under UV light at ca. 25 °C, all three trisulfides rearranged completely in 140–280 min, indicating a predominant change from a heterolytic thermal reaction to a homolytic photochemical one. These results indicated that the earlier polysulfide bissulfinates mentioned (i.e. **51**, $n = 4$, $m = 4$–5) probably contained some sulfide thiosulfonates such as **55**, and a caveat was published.[73]

7. SULFENIC ACIDS: SOME SURPRISINGLY STABLE DERIVATIVES

7.1. *Sulfenyl Halides*

Sulfenyl chlorides are mentioned elsewhere in several connections (cf. eqs. 6, 7 and Schemes 5–7, 12). Two features seem worth adding here: (1)[63] Reaction of 1-adamantyl disulfide with Cl_2 gave mixtures of unreacted disulfide, the sulfenyl chloride, and 1-chloroadamantane, although reaction at −24 °C instead of ca. 25 °C did increase the yield of sulfenyl chloride. On the other hand, use of SO_2Cl_2 at ca. 25 °C gave only the sulfenyl chloride (and SO_2). 1-Adamantanesulfenyl chloride, like most sulfenyl chlorides, should be used soon after preparation; at ca. 25 °C, 25–50% goes to 1-chloroadamantane in about an hour.[63] (2)[42] Several attempts to convert pentachlorobenzenethiol to the sulfenyl chloride were quite unpromising; however, based on work of Putnam and Sharkey, reaction of the thiol with Cl_2 in refluxing CCl_4 containing 5 mol % of iodine gave pentachlorobenzenesulfenyl chloride quantitatively; this intriguingly atypical sulfenyl chloride could be kept as a solid (m.p. ca. 100 °C) at 5 °C for many months, although in pentane solution decomposition at ca. 25 °C began within 0.3 h.[42]

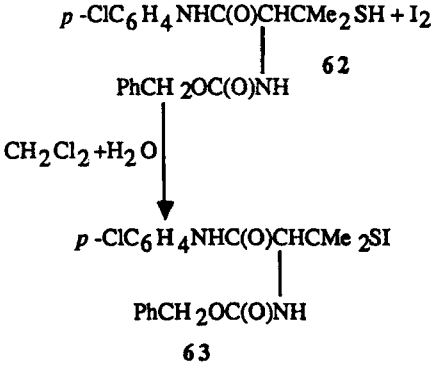
Our group spent much effort on sulfenyl iodides because of their apparent biological importance, for example in iodination of tyrosine to thyroxine in the thyroid gland;[74] details on the biological importance of sulfenyl iodides can be found in our review of sulfur-iodide bonds.[75] Our first efforts were made with 2-methyl-2-propanesulfenyl iodide (**60** of Scheme 10), which Rheinboldt and Motzkus had prepared 31 years earlier by



Scheme 10

the sequence of **56→57→60**.[74] We developed several syntheses to assure validity of spectroscopic conclusions that had not been feasible in the day of Rheinboldt and Motzkus: reaction of the sulfenamide **59** with HI and of the thiol (**56**) with ICl in CCl_4 or I_2 in CCl_4-H_2O (our preferred method), as well as the original addition of **57** to I_2 and the reverse.[74] Preparation of the unsymmetrical disulfide **58** and sulfenamide **59**, along with photolysis, confirmed the structure of **60** (Scheme 10). The characteristic UV absorption of **60** afforded a good means of assay. Under ambient conditions, only 50% of **60** in an inert solvent survived after three days, but at −12 °C in the dark most survived for 11 days; survival improved markedly with dilution.[74]

A sulfenyl iodide resulted also from the reaction of I_2 with triphenylmethanethiol but not with the thiolate salts of 1- or 2-butanethiol.[74] The evident stabilizing influence of tertiary structures led us to synthesize **63** (eq. 26), a pure crystalline solid that not only is a



(26)

model for protein sulfenyl iodides but, apart from these, appears to be the most stable sulfenyl iodide known; these results appeared in a preliminary communication,[76] followed by a full paper.[77]

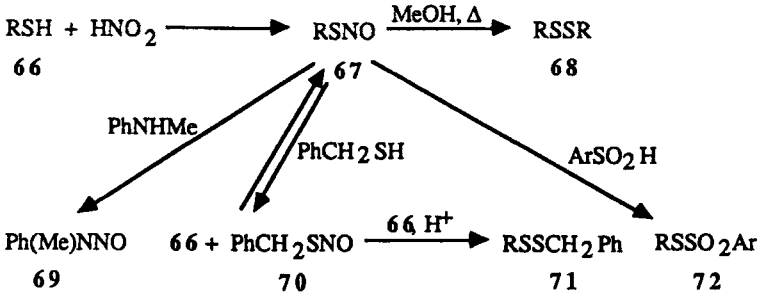
For the synthesis of **63**, the thiol **62** was oxidized with excess I_2, and the excess then was destroyed (eq. 26).[77] The yields of **63** were 94–100% in solution and 54% as yellow-brown crystals. Structural evidence included the stoichiometry of the oxidation, analyses (C, H, Cl, I, N, S), consistency of UV, IR, NMR, and mass spectra, and reactions like those of Scheme 10 in photolysis and to give unsymmetrical disulfides. Indeed, reaction with a thiol (or amine, which cyclized **63**) was so rapid that the colored solution of **63** could be cleanly titrated.[77] Such a reaction to give unsymmetrical disulfides nevertheless is not infallible, because when **64** was converted to the sulfenyl iodide **65** (X = I) the hoped-for conversion with thioacetic acid to **65** (X = SAc) actually resulted only in reduction back to **64** (eq. 27).[60]

$$\underset{\mathbf{64}}{\text{MeO(O)CCH(NHAc)CMe}_2\text{SH}} \underset{\text{AcSH}}{\overset{I_2}{\rightleftharpoons}} \underset{\mathbf{65}}{\text{MeO(O)CCH(NHAc)CMe}_2\text{SX}} \qquad (27)$$

As a solid, **63** began to decompose under ambient conditions only after ca. six months; a solution in CH_2Cl_2 was lost completely in about a week under ambient conditions but was unchanged after three months at −12 °C in the dark; an aqueous suspension had a half-life of ca. five days.[77] Complete photolytic decomposition required 30 h in contrast to only 2 h for 2-methyl-2-propanesulfenyl iodide (**60**).[77] All things considered, **63** is a rather stable but highly reactive compound.[76] Some of the cyclizations, such as that produced on standing in CH_2Cl_2 or by amines,[77] gave products of uncertain structure that seem likely to produce interesting results for someone looking further into them.

7.2. *Thionitrites*

Consistent with the facts mentioned that the tertiary hydrodisulfides **36**, **39**, and **40**, and the sulfenyl iodide **63**, are among the most stable of their species is the similar behavior observed with the normally unstable thionitrite species.[78] Thus, isolation was achieved of **67** as green crystals of mp 152–154 °C (dec.) in 63% yield (Scheme 11); **67** seems to be the most stable thionitrite so far found.[78] X-ray crystallography confirmed the structure and gave the first parameters for a SNO group.[78] Scheme 11 shows the behavior of **67**.[78]

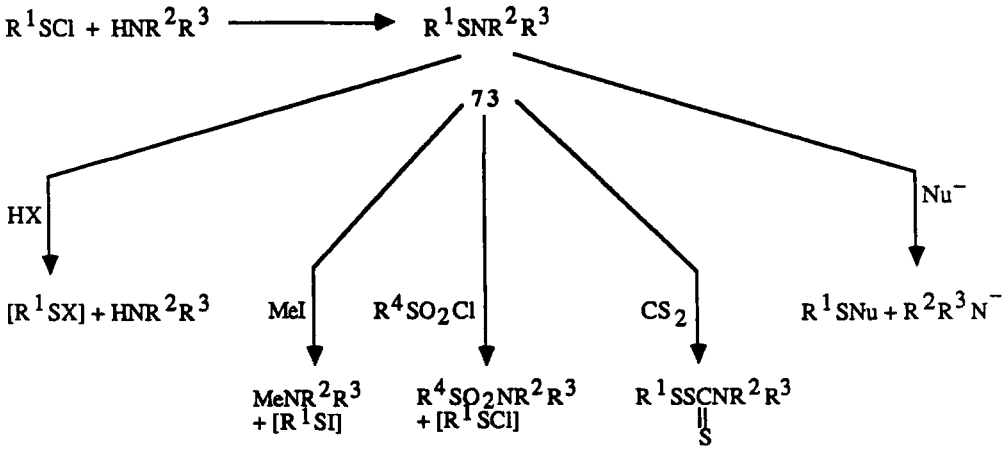


Scheme 11. R = $HO_2CCH(NHAc)CMe_2$.

Solid **67** was unchanged after ca. ten months but did go totally to the disulfide **68** after only 2 h in refluxing MeOH; in DMF, after 50 h at ca. 27 °C 95% of **67** survived in the dark and 67% in ambient light. The capability of homolysis for **67** was shown by induction of polymerization of methyl methacrylate and of heterolysis by nitrosation of *N*-methylaniline to give **69** and also by equilibration of NO between **66** and $PhCH_2SH$ to give **70** and (mostly) **66**.[78] Despite the latter equilibration, however, the disulfide **71** could be obtained in 42% yield.[44] A similar reaction with a sulfinic acid gave the thiosulfonate **72** in 61% yield.[44]

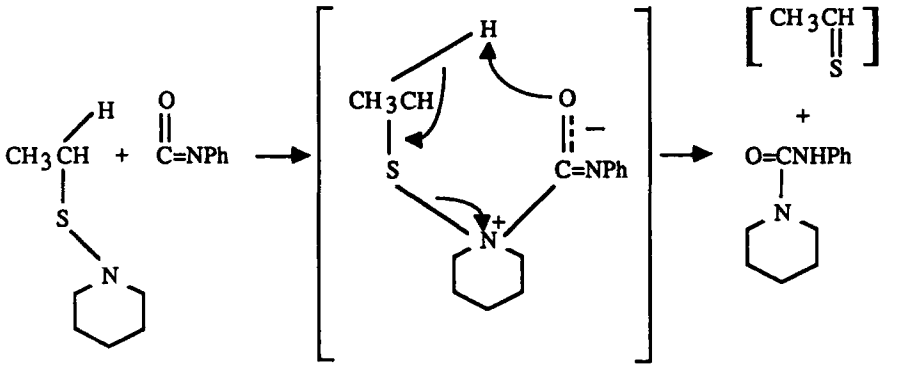
7.3. *Other Aspects*

Hydrodisulfides are sulfenyl derivatives in a sense; these were discussed already in Sec. 5.3.2. **Sulfenamides** (**73**) were studied extensively.[79] The smoothest synthesis was by reaction of sulfenyl chlorides with amines or amides (Scheme 12). Factors affecting stability, spectra, and other properties were assessed.[79] Thermal stabilities varied from a few minutes to several days at 100–155 °C, but all those studied were quite stable to



Scheme 12

light.[79] Particular attention was given to EI mass spectrometry, where the major fragmentations were C—S and N—S cleavages both with and without rearrangement of hydrogen; nearly all of the sulfenamides studied showed molecular ions. Reactions of sulfenamides with electrophiles usually give products consistent with attack on NR^2R^3, followed by cleavage of the S—N bond by an ensuing nucleophile; illustrative are the reactions of HX, MeI, R^4SO_2Cl, and CS_2 (Scheme 12; the bracketed intermediates then react further). However, isocyanates (and electron-deficient alkenes) react differently, as illustrated by Scheme 13. Reactions of



Scheme 13

sulfenamides with nucleophiles are illustrated by that with Nu^- in Scheme 12; for example, when Nu^- is a thiolate ion (R^5S^-) the products are R^1SSR^5 and $R^2R^3N^-$.[79]

8. SULFIDES

Most of our work with sulfides was incidental to other interests. One synthesis, piperidine-catalyzed addition of a thiol to an α,β-unsaturated ketone, is discussed in Sec. 15.2 (Scheme 25).[80] For prodrug purposes, piperidine also was used to catalyze addition to an α,β-unsaturated acid,[14] although in another similar instance addition was achieved without catalyst;[14] indeed, in still another instance of conjugation addition was better without catalyst (although in the latter instance, to our surprise, the alkylthio group ended up backwards, i.e. *alpha* to COOH rather than *beta*, because of unusual substitution by fluorine).[81] As a reminder, $BF_3{\cdot}Et_2O$ catalyzed addition of a thiol to a *non*conjugated system in Scheme 3 (63–74% yield).[9]

As for aryl sulfides, the bis(benzylthio) starting material of Scheme 1 was obtained by reaction of the dibromoarene with benzyl disulfide at 165 °C with Cu catalysis; the yield of $Ar(SCH_2Ph)_2$ was only 12%, but one bromine had been reduced off, so that a bonus of also-desired monosulfide ($ArSCH_2Ph$) resulted (37% yield).[7]

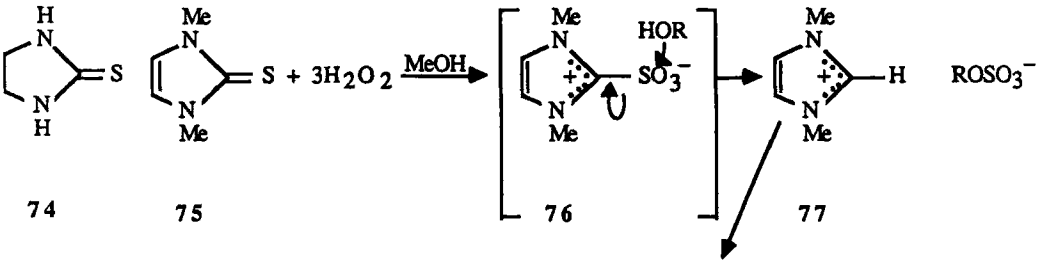
o-(Phenylthio)benzoic acid was needed for purposes explained in Sec. 10. It was best obtained by Cu_2O-catalyzed reaction of the dipotassium salt of 2-mercaptobenzoic acid with iodobenzene (88% yield),[82] but also nicely by the Cu_2O-catalyzed reaction of the salts of 2-iodobenzoic acid and thiophenol (82%); a third route, diazotization of 2-aminobenzoic acid and then Cu-catalyzed reaction with sodium thiophenolate, gave a 61% yield.[82]

Debenzylations of benzyl sulfides to thiols were formulated above with $AlBr_3$ (Scheme 1) and Na/NH_3 (Scheme 3).

9. THIOCARBONYL AND OTHER THIONO COMPOUNDS

9.1. *Thiocarbonyl Compounds*

The oxidation of thioamides and the mutagenicity of thioacetamide *S*-oxide were discussed in Sec. 3. Since 2-imidazolidinethione (**74**) joins thioacetamide in being carcinogenic, we did considerable research on oxidation of thiono imidazoles and their derivatives.[83] Oxidation of the thiono imidazole **75** gave the salt **77** (which was isolated as the picrate), along with sulfate ion (Scheme 14, R = H).[83] Of several possible routes (in which free



Scheme 14

radical reactions and the dioxide may be important), the route of Scheme 14 seemed the most attractive.[83] Similar results occurred with the ring-saturated counterpart of **75**. As in Scheme 14 where R = Me, formation of $MeOSO_3^-$ from solvent methanol both supported the route of Scheme 14 and the likelihood that biological damage might be explained by attack of nucleophilic biomacromolecules on structures like **76**.[83] The *N,N*-diphenyl counterpart of **74** was much less readily oxidized than **75** or its ring-saturated counterpart; it gave the compound in which O merely replaced S.[83]

The behavior of thiobenzophenone in the Darzens reaction is discussed later (Sec. 15.1), as is the photolytic conversion of carbonyl sulfide (COS) to carbon monoxide and monoatomic singlet sulfur, $S(^1D)$ (Sec. 17). Here it might be said, however, that the latter work showed that singlet sulfur, $S(^1D)$, could convert a thiol to a hydrodisulfide,[84] paralleling a reaction believed to explain damage to thiol-containing enzymes by $S(^1D)$ formed by oxidation of thiono phosphorus compounds, as discussed next. Nevertheless, we concluded that reactions of $S(^1D)$ probably did not explain the biological damage, because oxidations of a thiono phosphorus compound in the presence of known traps for $S(^1D)$ did not lead to any trapping.[85]

9.2. *Oxidation of Thiono Phosphorus Compounds*

Phosphorothioates, such as the insecticide parathion (**78**, R^1 = Et, R^2 = *p*-$O_2NC_6H_4$), are widely used but produce adverse biological effects that seem to

be caused by intermediates from biological oxidation.[85-87] In the hope of clarifying such causes, we investigated

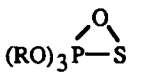
$$(R^1O)_2\overset{S}{\overset{\|}{P}}OR^2 + 4\ 3\text{-}ClC_6H_4CO_3H \longrightarrow (R^1O)_2\overset{O}{\overset{\|}{P}}OR^2 + 4\ 3\text{-}ClC_6H_4CO_2H + SO_3 \quad (28)$$

78 MCPBA (with H_2O as H_2SO_4)

oxidations of thiono phosphorus compounds at length. The initial results appeared in a communication,[85] followed by two full papers.[86,87]

The first full paper dealt mainly with spectra.[86] When a phosphorothioate (**78**) was oxidized with *m*-chloroperoxybenzoic acid (MCPBA, eq. 28) to the product where O replaced S, a vigorous reaction occurred at 25 °C, and no intermediates were detectable.[85] Below 0 °C, however, intermediates were discernible by spectra, and the lifetimes could be determined by ^{31}P NMR.[85,86] New major peaks appeared in a range of 13–33 ppm, between those for the P = S and P = O functions.[86] Lifetimes varied from a few minutes to many hours;[86] they were much longer with the esters (**78**, **79**) than with thiophosphoramides (**80**, **81**) and with aryl groups (especially containing electron-donating substitutents) than with alkyl groups.[86] The stoichiometry and products of the reaction were consistent with eq. 28 for the reaction.[85]

$(RO)_3P{=}S$ (**79**) $(RO)_2\overset{S}{\overset{\|}{P}}NHAr$ (**80**) $(RNH)_3P{=}S$ (**81**)



$(RO)_3P(S,O)$ (**83**)

Scheme 15

Earlier investigators had proposed phosphoxathiiranes (**82**) as intermediates,[85,86] and these indeed might be involved (as might the noncommittal transition state **83**).[86] But the major intermediates actually identified turned out to be the very intriguing phosphonium polysulfides of structure **84** (eq. 29).[86,87] Mass spectra indicated that *x* of **84** could be as high as 7, presumably with the sulfur atoms in a straight chain.[87] UV spectra supported structure **84**,

$$2\,(RO)_3PS_x \xrightarrow{\textbf{78 or 84}} (RO)_3PS_nP(OR)_3 \quad (29)$$

84 **85**

since absorptions at wavelengths exceeding ca. 325 nm typical of polysulfides appeared and then disappeared.[86] Formation at ca. 25 °C of a little elemental sulfur was accounted for by cyclization of the polysulfide chain of **84**. At low temperatures, reactions such as the formation of **84** and **85** predominated; some persistence of spectra indicated ultimate formation of a certain amount of **85** by reaction of **84** with itself or with starting material (eq. 29).[86,87]

The second full paper dealt mainly with reactions of intermediates.[87] HPLC separated unstable intermediates for which UV and mass spectra supported structure **84**. That intermediates like **84** reasonably could cause biological damage by acting as thiolate-type nucleophiles was illustrated by addition to *N*-ethylmaleimide and other Michael-type acceptors, as well as by attack on Ellman's reagent (a disulfide that RS^- attacks to expel a spectrochemically characteristic thiolate ion).[87] That such intermediates additionally might cause biological damage by acting as electrophiles was evidenced by reaction with trimethyl phosphite (eq. 30) and other nucleophiles.[87] Accordingly, it seems likely that sulfane

$$(MeO)_3P + \mathbf{84} \text{ or } \mathbf{85} \longrightarrow (MeO)_3PS \qquad (30)$$

intermediates such as **84** (or perhaps R_3POS_x) might exert adverse biological effects *either* by attacking biomacromolecules as nucleophiles *or* or by being attacked as electrophiles.[87]

9.3. *Mutagenesis and Carcinogenesis by Thiono Phosphorus Compounds*

We found that the well known anticancer drug thio-TEPA (**86**) inhibited growth of four human tumors *in vitro*.[88] With three of these, **86** was effective only at concentrations that

86 (thio-TEPA) **87** (TEPA)

also caused mutagenesis in the standard Ames assay.[88] With the fourth tumor, on the other hand, **86** inhibited tumor growth at concentrations that did *not* induce mutagenesis. It thus seems feasible in treatment of a particular type of tumor to seek an agent that can selectively inhibit its growth without also causing mutagenesis.[88]

It is noteworthy that thio-TEPA (**86**) causes mutagenesis in the Ames assay only after biological activation.[88] Presumably it requires oxidation to TEPA (**87**), which is mutagenic without activation because the electronegative oxygen atom enhances susceptibility to attack by biological nucleophiles.[88]

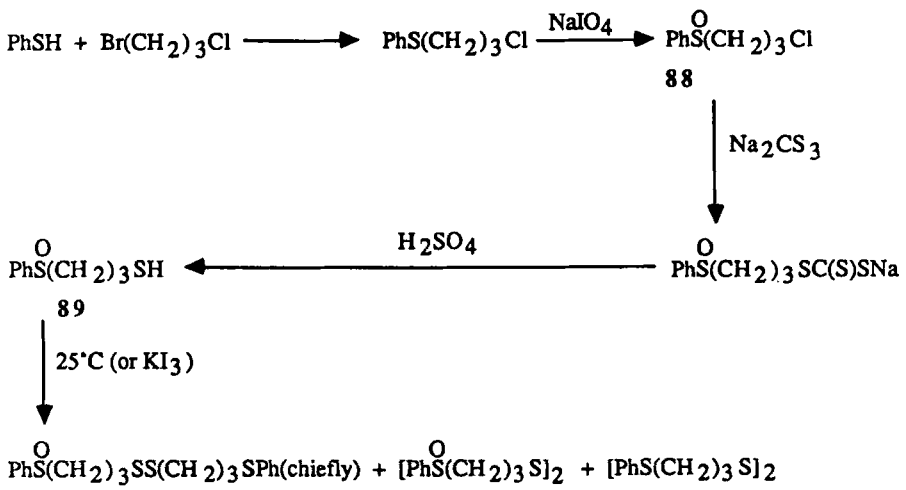
A structure-activity correlation of various phosphorothioate esters of structures **78** and **79** showed that mutagenic ones contained one group that was strongly electron withdrawing and/or a good leaving group, along with two others small enough to permit facile attack on the phosphorus atom by a nucleophilic bio-

macromolecule.[89] For mutagenesis, all but one of the esters required metabolic activation. Since an assay for carcinogenicity showed that only one of six mutagenic esters was carcinogenic, carcinogenicity may accompany mutagenicity but does not necessarily do so.[89]

Ames assay of thiophosphoramides (**80**, **81**) led to guidelines for mutagenesis much like those deduced for the esters.[90] However, since only three of eight amides were mutagenic (and then only marginally at high concentrations) in contrast to unquestionable mutagenicity with six of eleven esters, mutagenic hazards seem likely to be less with the amides.[90]

10. SULFOXIDES

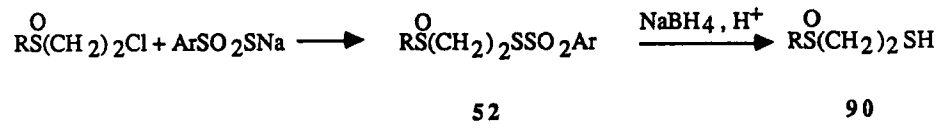
Interest in the compatibility of thiol and sulfoxide functions (which are known to oxidize thiols), as well as in sulfinylalkyl disulfides (Sec. 5.3.3), led us to study mercaptoalkyl sulfoxides.[65] Scheme 16 shows the synthesis of **89**, the first representative of this bifunctional class.[65] In methanol, the half-life for the first-order disproportionation of **89** to the products shown was 5.0–5.8 h, although **89** could be kept longer than a week neat or in chloroform.[65]



Scheme 16

An interesting sidelight was that even the chloro sulfoxide **88** disproportionated, to the sulfide and sulfone, although only during several months.[65]

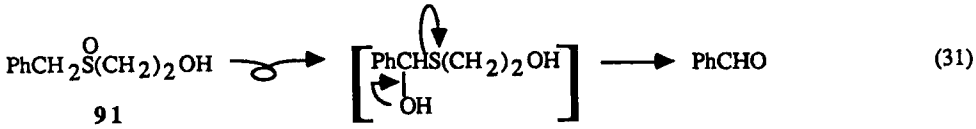
Disproportionation with the arylsulfinyl thiol **89** led us to look at the alkylsulfinyl thiol **90**.[66] Scheme 17 shows the synthesis. With only a little $NaBH_4$, the disulfide of **90** resulted, but an excess with the disulfide followed by acidification gave **90**; **90** was



Scheme 17. R = $PhCH_2$.

isolated by precipitating the mercuric thiolate and treating it with H_2S.[66] The thiol **90** was even less stable than **89** and could be kept only for a few minutes; for example, the yield of **90** was 58% after 5 min but dropped to 13% in less than 2 h.[66] The rapid loss of **90** seemed to occur by the same kind of disproportionation encountered with **89**.[66]

The work with **90** led in turn to the benzyl sulfoxide **91**.[91] In contrast to a reported b.p. of 167 °C (0.3 torr), heating completely destroyed **91** and gave up to 41% of benzaldehyde (eq. 31), along with some incidental things. The OH group was not required, since benzyl *n*-propyl sulfoxide gave up to a 49% yield of benzaldehyde. There



(31)

were hints in the literature that supported the occurrence of a Pummerer reaction, as formulated in eq. 31. The reaction seems to be catalyzed by acid generated early in the thermolysis.[91]

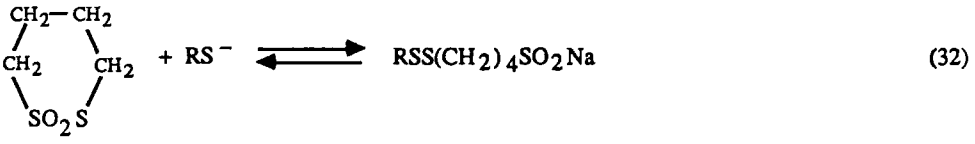
Another interest in sulfoxides originated in our arguments that appropriately structured ones might be useful counterparts of medicinally important amines.[82] Furthermore, with a few notable exceptions such as DMSO, sulindac, and sulfinpyrazone, sulfoxides seem to have received less attention medicinally than they may deserve. The synthesis of *o*-(phenylthio)benzoic acid was discussed earlier (Sec. 8). Its sulfoxide was intended to be an analog of fenamates, a class of *o*-(arylamino)benzoic acids active as antiinflammatory agents. This product was inactive, but 2-(carboxymethyl)phenyl phenyl sulfoxide was roughly comparable to aspirin.[82]

11. SULFINIC ACIDS AND DERIVATIVES

11.1 *Acids and Salts*

Quite a bit of this work has been mentioned already, or will be dealt with later. Thus reactions of acyclic thiosulfonates with thiols to give sulfinic acids and disulfides were discussed (Sec. 5.1; cf. eq. 10), as were applications to cyclic thiosulfonates (Sec. 5.3.1; cf. eq. 19). We applied the approach of eq. 19 extensively to synthesize butanesulfinates terminated by disulfide functions, as shown by eq.

32; the tri- and pentamethylene congeners similarly gave propane- and pentanesulfinates terminated with disulfide

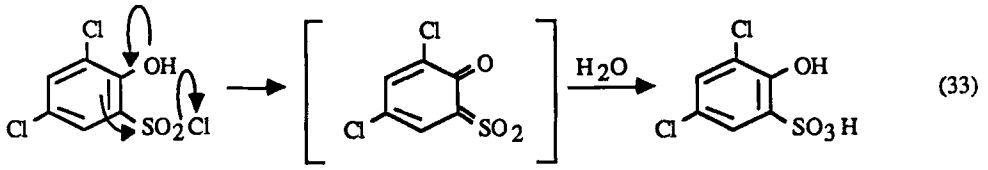


(32)

R = substituted alkyl, alicyclic, aryl, or heterocyclic groups[37,49,51,52,55]

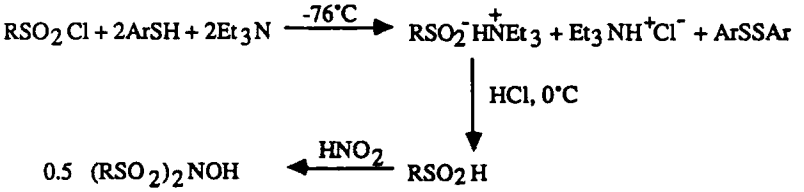
functions.[49,52] Synthesis of tri- and polysulfide sulfinates by like means were discussed in Section 6 and illustrated with eq. 23.[52,53,72] As also mentioned, in such reactions sulfinate salts usually were isolated by precipitation from an alcohol used as solvent for the reaction, followed by reprecipitation (cf. Sec. 5.1).[37,51,52,55,72] Preparation of 2-substituted ethanesulfinates will be discussed in Sec. 15.1 (eq. 52).

Sodium sulfite usually nicely reduces arenesulfonyl chlorides[92] or alkanesulfonyl chlorides[93] to sodium sulfinates. So, we were startled when an *ortho*- or a *para*-hydroxybenzenesulfonyl chloride gave hydroxybenzenesulfonates as the chief or sole product, despite much struggle.[92] At first, we blamed simple hydrolysis. Ultimately, several lines of evidence convinced us that the cause was intervention of aryl counterparts of sulfenes (monothioquinone *S*,*S*-dioxides), as eq. 33 shows;[92] checking then revealed that others also had proposed such structures.



(33)

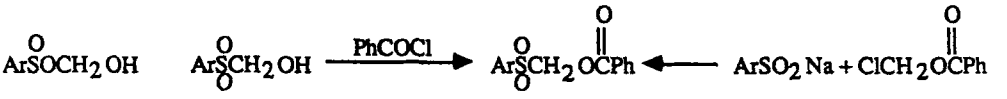
The initial purpose of our work with hydroxy sulfinates, to connect them by ester linkages to carboxy disulfides to give sulfinate-disulfides for biological uses, finally was achieved in several ways that need not be recounted here.[92,93] At this point, in any event, we still needed hydroxyarenesulfinic acids. The route shown in Scheme 18 was developed as the most successful of many tried.[94] Scheme 18 took advantage of what has long been considered a nuisance side reaction, i.e. formation of disulfides when a thiosulfonate is



Scheme 18

sought from reaction of a sulfonyl chloride and a thiol (the thiosulfonate produced thioalkylates the thiol). The adaptation of Scheme 18 afforded a rapid, mild, selective, convenient, and general method, not only for converting hydroxyarenesulfonyl chlorides to sulfinates but for many other types of sulfonyl chlorides as well; yields for 18 quite varied examples were 51–92%.[94] Titration with nitrous acid by a procedure of Marvel and Johnson (Scheme 18) showed purities of 95–100% (characterizations also were achieved by spectra and through *S*-benzylthiuronium salts or *p*-nitrobenzyl esters).[94]

A question much like one settled earlier (that adducts of aldehydes with sodium bisulfite are α-hydroxy sulfonates and not α-hydroxy sulfites) was whether the adduct of formaldehyde with *p*-toluenesulfinic acid had structure **92A** or **92B**. That **92B** is correct was settled by conversion to the benzoate, which was unambiguously and independently synthesized (Scheme 19).[95]



92A **92B**

Scheme 19

11.2. *Esters and Sulfinyl Chlorides*

Sulfinic acids usually are easily oxidized and also disproportionate readily. With the salts, hydration leads to a lot of trouble in handling and often causes analytical problems.[24,37,51–53] Sulfinic esters are of interest for minimizing these frustrating difficulties.

Oxidation of aromatic and heterocyclic disulfides with lead tetraacetate (LTA) in the presence of an alcohol afforded a nice synthesis of sulfinic esters (eq. 34);[96–98] the alcohol could be primary, secondary, or tertiary.[97] Thiols also could be used, since LTA oxidizes

$$\mathrm{ArSSAr} + \underset{\text{LTA}}{3\mathrm{Pb(OAc)_4}} + 4\,\mathrm{AlkOH} \longrightarrow 2\,\mathrm{ArS(O)OAlk} + 3\,\mathrm{Pb(OAc)_2} + 4\,\mathrm{AcOH} + 2\,\mathrm{AcOAlk} \tag{34}$$

them cleanly to disulfides (eq. 11).[97] It is worth adding that liquid sulfinic esters underwent rapid hydrolysis under ambient conditions (cf. also ref. 101), but that solid esters held up rather well.[97] Oxidation of dialkyl disulfides with LTA unfortunately was unpromising, although methyl 1-pentanesulfinate could be prepared in yields up to 35%.[99]

Appropriate disulfides thus afford a nice route to sulfinic esters. However, the question still remained of how best to esterify sulfinic acids or salts obtained by other routes. One method we developed, perhaps still the best for alkanesulfinic

esters, was to acidify a sodium alkanesulfinate in MeOH with dry HCl and then to use diazomethane.[55,100] Another method, based on work of Kobayashi, was to use trialkyloxonium fluoborates with sulfinic acid salts,[100-102] and still a third method was to use $BF_3 \cdot Et_2O$ as a catalyst with either a sulfinic salt or acid in the alcohol containing dry HCl (the HCl was not always necessary).[101]

Finally, we developed a method for preparing stable crystalline sulfinate esters.[103] The most promising alcohols were 1-adamantanol and *p*-nitrobenzyl alcohol. Either a sulfinic salt or acid could be coupled with these and other alcohols by using chlorotrimethylsilane, but the most attractive procedure was to acidify the sulfinate salt with dry HCl in THF and then to couple the alcohol by means of 1,1-carbonyldiimidazole.[103] Mixed success was encountered for alkanesulfinate synthesis, however, and phenols or thiols could not be used satisfactorily in place of alcohols.[103]

Any who seek analogies for preparation of alkyl sulfinates from conventional use of sulfinyl chlorides may find refs. 4 and 104 helpful. In the latter work,[104] to our surprise we could not obtain the sulfinyl chloride **93** by the previously reported reaction of eq. 35. Suspecting that a catalytic impurity had made the reported reaction possible, we finally tried

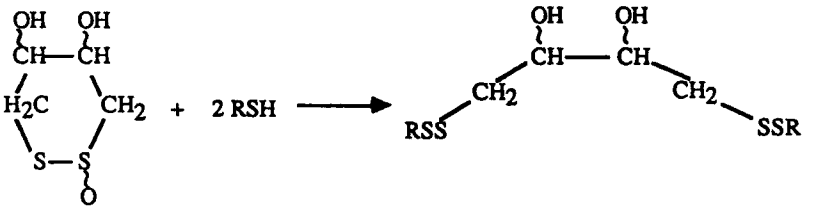
$$HS(CH_2)_2CO_2H \xrightarrow{Cl_2} [-S(CH_2)_2CO_2H]_2 \xrightarrow{Cl_2(SCl_2)} ClS(CH_2)_2\overset{O}{\underset{}{C}}Cl \qquad (35)$$

93

adding 5 mol % of sulfur dichloride, which we thought likely as an impurity, and were delighted to get **93** in good yield. Incidentally, **93** was too unstable to be purified readily, but we could characterize it as the amide, by titrating **93** with $KMnO_4$, and by titrating the corresponding acid with HNO_2.[104] As a general comment, one wonders from this experience if earlier results of various kinds by others that cannot be repeated also might stem from unsuspected catalytic impurities that could be guessed and tried.

11.3. *Other Sulfinic-acid Derivatives*

The formation of two disulfide functions by reaction of a cyclic **thiosulfinate** with two molecules of thiol (rather than only one with thiosulfonates) was illustrated with **21** (Sec. 5.1). An interesting variant with one more sulfur in the ring was **46**, which was shown in Scheme 9. Both **21** and **46** were synthesized by oxidizing the respective di- and trisulfides with sodium perborate.[41] Oxidation of 1,2-dithiane-4,5-diols to the cyclic thiosulfinates presented considerably more of a problem, but eventually H_2O_2 was satisfactory, when tungstic-acid catalysis and some special tricks were used.[39] The four stereoisomers of these cyclic thiosulfinates also reacted characteristically with two molecules of thiol (eq. 36).[39]

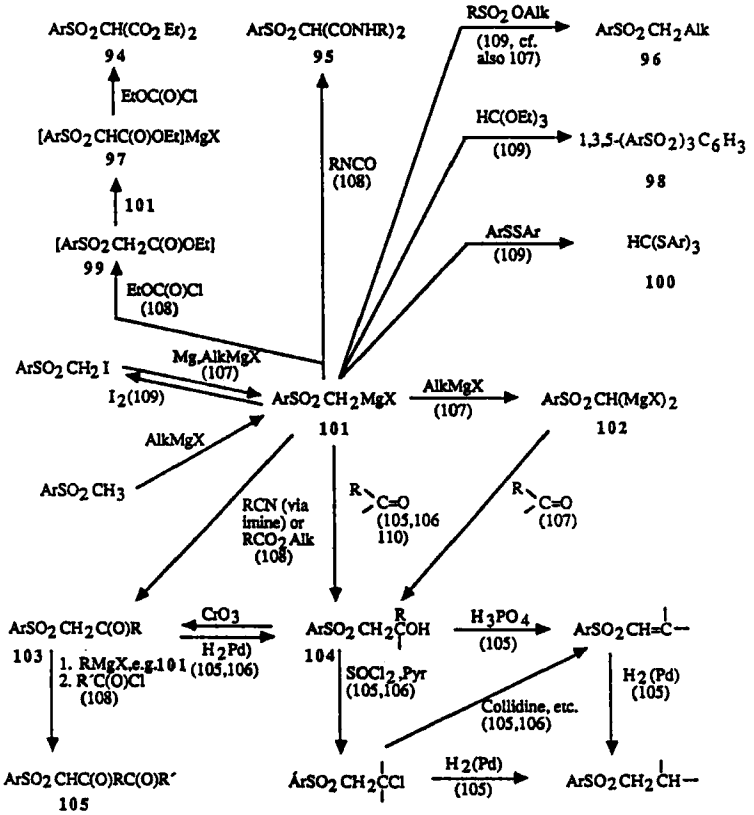


(36)

Synthesis of 2-mercaptoethanesulfinic acid salts is illustrated later (Sec. 15.1; eq. 52); these could be converted to sulfinate disulfides and to various sulfones.[100]

12. SULFONES

Some half-dozen research groups had worked with "Grignard reagents of sulfones," i.e. α-halomagnesioalkyl derivatives such as **101** of Scheme 20, but largely as incidental to



Scheme 20. Products shown, where appropriate, were obtained after acidification of organometallic intermediates. The reference for each reaction is shown in parentheses.

other research.[105] Our interest was drawn to this class by finding that although in many ways reagents like **101** behaved like typical Grignard reagents, and hence promised to be useful for many then new kinds of syntheses, in many other ways they were intriguingly different. As examples in Scheme 20 show, the product (**101**) obtained by metalating a methyl aryl sulfone with an alkylmagnesium halide (with loss of the alkane) reacted typically with carbonyl compounds, and the adducts (**104**) could be converted nicely to new carbonyl compounds (**103**), β-chloroalkyl sulfones, unsaturated, or saturated sulfones; several of the reactions in Scheme 20, along with many others, were done to nail the structures down firmly.[105] Ketones reacted, as did aldehydes, even a hindered one like diisopropyl ketone,[106] although one like *p,p'*-dichlorobenzophenone was sluggish.[110]

With an acyl halide such as ethyl chloroformate (Scheme 20),[108] acylation of half of the **101** used gave **99**. Metalation of **99** by the remaining half of the **101** gave **97**, which the acyl halide was reactive enough to acylate a second time. The product therefore was the sulfonylmalonate **94**.[108] An isocyanate behaved similarly and gave a malonanilide (**95**).[108] On the other hand, esters are less reactive and, although the intermediary monoacylated sulfone (**103**) from **101** was metalated in the same way by **101** as was **99**, so that half of the sulfone was regenerated, the ester was insufficiently electrophilic to react a second time; the product after the usual acidification therefore was the monoketosulfone **103**.[108] This lack of reactivity after metalation of a β-keto sulfone is typical with Grignard reagents in general and probably reflects a degree of enolate character for intermediates like **97**; for example, when a keto sulfone (**103**) was treated with excess EtMgBr, acidification regenerated **103** and no carbinol was seen.[108] As might be expected on the other hand, benzoyl chloride will benzoylate the halomagnesium intermediate from **103**, thus predicting a useful synthesis of a methyl sulfone containing two different acyl groups (e.g. **105**), by reaction with **101** of an ester, followed by an acyl halide.[108] Nitriles, like esters, reacted only once; the intermediate imine could be isolated and then hydrolyzed to the keto sulfone **103**.[108] Nothing ever was observed to indicate that three groups could be introduced on the same carbon atom under any circumstances,[108] although use of bases might be worth trying where a metal (lithium?) could stabilize a product such as a carbinol by strongly associating with it.

In other reactions (Scheme 20),[109] iodine converted **101** to the α-iodo sulfone, an alkyl tosylate (or a benzyl halide) alkylated **101** to give **96**, ethyl orthoformate gave a 1,3,5-tris(arylsulfonyl)benzene (**98**), and a disulfide gave a trithioorthoformate (**100**).[109] The reader is challenged to compare mechanisms for the formation of **98** and **100** with those published.[109]

At about the time the disulfide reaction was under study, the utility of *n*-butyllithium was being made clear in other laboratories, and indeed we found that *p*-tolylsulfonylmethyllithium produced by using it gave a better result than **101** in the disulfide reaction.[109] It seems likely that lithium counterparts of **101** may give better results in some of the other reactions as well. However, the reverse also can be true,[109] and I have a hunch that Grignard reagents of sulfones will have advantages of selectivity, stereochemical characteristics, complexations,

etc., that well warrant further study and that will make it worthwhile not to write this class off in invariable favor of α-lithioalkyl sulfones.

α-Halomagnesium compounds from ethyl and isopropyl aryl sulfones reacted like **101** with carbonyl compounds (although steric hindrance precluded reaction of the isopropyl product with diisopropyl ketone).[106]

Dimethyl sulfone could be monometalated; the product then reacted with benzaldehyde, although products from dimetalation reduced the yield to 33%.[106] α,ω-Alkylene disulfones, $ArSO_2(CH_2)_nSO_2Ar$, apparently could be metalated at the α and α′ positions where n = 3–5, but elimination predominated with n = 2; with n = 5, products reacted as usual with bromine and carbonyl compounds, although isolated yields were modest.[111]

All told, one can synthesize a wide variety of sulfones by using reactions like those of Scheme 20. This fact led us to try to make methyl *p*-tolyl sulfone more readily available for such purposes; we were able to combine some existing procedures and develop them, with the result shown in eq. 37.[112,113]

$$\underline{p}\text{-}CH_3C_6H_4SO_2Cl \xrightarrow{Na_2SO_3} \underline{p}\text{-}CH_3C_6H_4S(O)ONa \xrightarrow{(MeO)_2SO_4} \underline{p}\text{-}CH_3C_6H_4SO_2CH_3 \qquad (37)$$

Unfortunately, none of our experiences with the reactions of Scheme 20 indicated that the sulfone group might be removed from products in such a way as to afford useful syntheses of a variety of *non*sulfur compounds. Also, the literature indicated that sulfonyl-carbon bonds were quite refractory and that it would be synthetically impracticable to try to break them. Such cleavages of course since have been shown to be quite useful by many investigators and, as two of my reviews eventually attested,[114,115] a wide variety of reducing agents now are well known to replace sulfonyl groups nicely by hydrogen atoms. Removal of sulfonyl groups by elimination-type reactions also is a useful tool.[115] The moral of our missed opportunity to develop useful nonsulfur syntheses, I suppose, is that one shouldn't pay too much attention to "it can't be done" in the literature.

We wondered about the extent to which the two hydrogen atoms remaining on **101** could be replaced. As Scheme 20 implies, gas evolution indicated that a second hydrogen indeed could be replaced, to give **102**, although for reasons unclear to us (but with precedent), benzaldehyde reacted with **102** only once, to give **104**;[107] as the corollary one therefore might expect, treatment of **104** with excess EtMgBr and then benzaldehyde led after acidification only to recovery of the **104**.[110] Efforts to replace all three hydrogens resulted in considerable reduction and formation of thiophenol and no useful product.[107]

The properties of Grignard reagents of sulfones are fascinating. Overall, they seem better regarded as weakly nucleophilic Grignard reagents than as carbanion salts;[109] for example, **101** could be alkylated by *n*-hexyl *p*-toluenesulfonate as can Grignard reagents but not at all by *n*-hexyl iodide as can a carbanion salt.[109] The order of reactivity of **101** seems comparable to that of phenylmagnesium bro-

mide.[106] On the other hand, reagents like **101** show negligible tendency to disproportionate as do typical Grignard reagents, perhaps because of another notable difference, their virtual insolubility in diethyl ether.[107] They can be isolated as white powders that look like flour, that are unsolvated by ether, and that have good thermal stability.[107] They could not be made merely by reaction of an α-halomethyl sulfone with magnesium, although reaction did succeed upon "entrainment" with ethyl bromide.[107] A key reason for some of these atypical behaviors seems to be that the MgX of one molecule associates with the $—SO_2—$ of an adjacent one until a polymeric aggregate results.[107] In support of this idea, ethereal EtMgBr will form a precipitate with diphenyl sulfone,[107] and **101** will dissolve in benzene containing a large excess of ethereal EtMgBr presumably because association of **101** then occurs with EtMgBr rather than with itself.[111] Formation of polymeric aggregates would explain the insolubility, the lack of ether solvation of the already associated molecules, and (because of covering of active spots) the lack of reactivity with magnesium not only of α-halo sulfones, but also of β-halo sulfones, of sulfones that contained an allylic halogen atom (quite reactive in metathetical reactions), or even of a 1,1-dimethyl-4-halobutyl aryl sulfone with no α-hydrogen and with removal of the halogen to the δ position.[107] This explanation of a small amount of inhibitory covering of "hot spots" on magnesium is supported by the facts that ethers, tertiary amines, and pyridines also form addition compounds with Grignard reagents and that such halo derivatives usually react difficultly or not at all with magnesium, a feature attributable again to coating of "hot spots" by polymeric aggregates;[107] it would be interesting to confirm the possibilities of polymeric association with Grignard reagents of these kinds.

In recent years, negligible attention has been given to Grignard reagents of sulfones because of availability of the lithium counterparts. However, I suspect that rich harvests still may be available with this class. Some other aspects of the chemistry of sulfones will be related in the next section, 13, on sulfonic acids.

13. SULFONIC ACIDS AND DERIVATIVES

13.1. *Acids and Salts*

A foray into sulfonic-acid chemistry led to synthesis of α-amino-(β-benzylthio)ethanesulfonic acid, one of relatively few α-aminoalkanesulfonic acids then known.[116] It was obtained by treating the bisulfite addition product of β-(benzylthio)acetaldehyde with NH_4OH and then acidifying. Although it decomposed rather easily in hot water, it was relatively stable as a solid.[116] Other interests diverted us from using this product for making cysteine analogs; somehow, we never got back, but even now this prospect seems worth someone's attention.

The interesting attributes of lead tetraacetate (LTA) led us to explore reactions of corresponding sulfonic-acid salts of tetravalent lead.[117] We usually prepared these *in situ* by displacing acetic acid from LTA with the much stronger sulfonic

acids. In reactions like those of LTA, lead tetratriflate cleaved benzopinacol to benzophenone (80% yield), and lead tetramesylate converted diethyl malonate to diethyl methylsulfonyloxymalonate (67% yield); methyl acetoacetate, ethyl cyanoacetate, and even benzene similarly could be sulfonyloxylated, although in lower yield (malononitrile gave an unstable product).[117] As with LTA (eq. 34), lead tetramesylate in the presence of an alcohol oxidized disulfides to sulfinic esters, but LTA affords the better route.[117] Lead tetrasulfonates thus proved to be reasonably selective and promising oxidants, but such powerful ones that a problem is to minimize their self-destruction and their overoxidation of substrates.[117]

13.2. *Halides and Anhydrides*

In connection with other interests, we developed the first synthesis of alkanesulfonyl iodides.[118] As an example, treatment of sodium methanesulfinate with aqueous KI_3 gave a green-black precipitate of methanesulfonyl iodide in 82% yield.[118] Under reduced pressure, this iodide evolved iodine readily, but it was sufficiently stable to be synthetically useful.[118]

Sulfonic anhydrides have received less attention than they deserve. For instance, when sulfonate esters are made from sulfonyl halides, the halide ion produced may be nucleophilic enough to displace the sulfonate ion and thereby convert the sulfonate to a halide. On the other hand, the sulfonate counterion produced from an anhydride, being much less nucleophilic, is much less likely to destroy the desired ester. In order to study anhydrides, we developed a simple economical synthesis, which consists simply of heating the acid (or its hydrate) with P_2O_5 in the presence of inert material that will facilitate extraction.[119-121] Since sulfonyl chlorides often are more accessible than the acids, we also developed a practical synthesis from the chlorides, in which these were heated with yellow mercuric oxide.[121]

p-Toluenesulfonic anhydride (**106**) has an astonishingly broad melting range.[119] The reasons for the broad range seem to be a rather high freezing-point depression constant

$$(p\text{-}H_3CC_6H_4SO_2)_2O \qquad (CH_3SO_2)_2O$$

106 **107**

and the low melting point of *p*-toluenesulfonic acid, the usual impurity;[119] only 1.7% of the acid depresses the softening point of the anhydride by 40 °C.[121] The anhydride **106** gave better results than the chloride in the sulfonylation of diethyl sodiomalonate and in the conversion of a thiol to a thiosulfonate.[119] Sodium sulfite reduces benzenesulfonic anhydride (as it does the chloride) to sodium benzenesulfinate.[119]

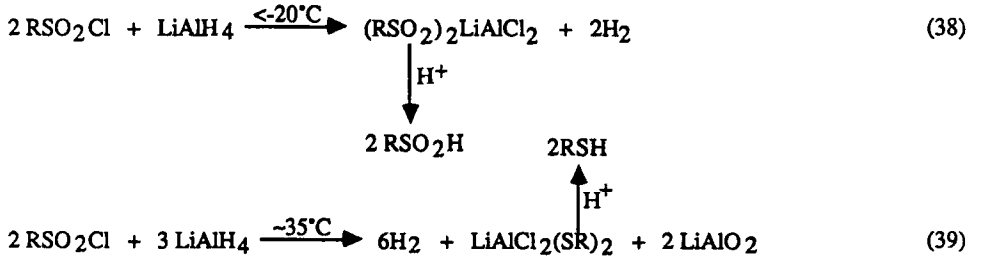
Another example of an advantage of the anhydride over the halide is that methanesulfonic anhydride (**107**) gives a much better synthesis of methanesulfonyl isocyanate with silver cyanate than does the chloride.[121] It also promotes

esterification of acetic or benzoic acid,[121] probably by formation of a sulfonic-carboxylic anhydride, from which the stronger sulfonic acid is expelled upon reaction with hydroxyl groups; this route provides a convenient mild means of esterification of carboxylic acids.

With both **106** and methanesulfonic anhydride (**107**), Friedel-Crafts type syntheses of sulfones are faster and/or better than with chlorides.[119,121] Pyridine gives 1:1 complexes that readily form sulfonate esters of phenols; such complexes dissolve immediately in water and are hydrolyzed so easily that this reaction affords a convenient means of destroying excess anhydride.[119,121] Reactions of **106** and **107** with Grignard reagents seemed complex and unlikely to be useful.[119,121]

Hydrogen chloride or bromide cleave **107** to give the methanesulfonyl halide.[122] With benzenesulfonic anhydride, on the other hand, HBr causes a reduction to diphenyl disulfide, which then is brominated by the bromine formed as an oxidation product to give bis-(*p*-bromophenyl) disulfide.[119]

When lithium aluminum hydride first appeared on the scene, our curiosity was aroused as to advantages it might afford for sulfur chemistry. Indeed, we found that it reduces an arenesulfonyl chloride or sulfonic anhydride selectively to either a sulfinic acid or thiol, depending on the conditions.[123] Its further selectivity was shown by reduction of β-styrenesulfonyl chloride to the β-styrenesulfinate in 78% yield.[123] The stoichiometry of the halide reactions was consistent with eqs. 38 and 39.[123] Not surprisingly, a rash of papers on reactions of the



(38)

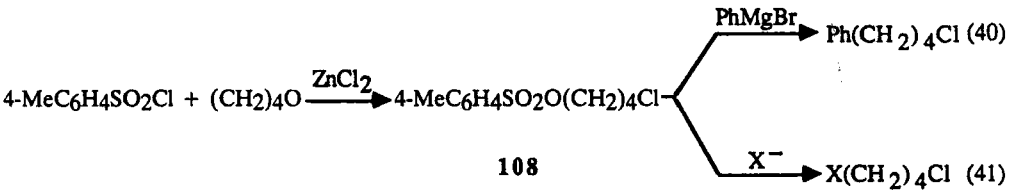
(39)

new reagent with various classes of sulfur compounds appeared at about the same time as ours, again illustrating the well recognized point that when something new appears on the horizon, one needs either to move fast or prepare to be "scooped."

13.3. *Esters and Amides*

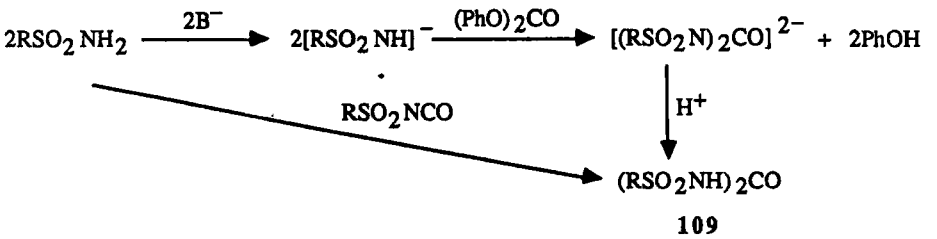
ω-Haloalkyl sulfonates, $RSO_2O(CH_2)_nX$, had been recognized as attractive alkylating agents where n = 2 to 3, because the terminal halogen atom is available for subsequent reactions (cf. ref. 124). We thought we might contribute the counterpart where n = 4 (**108**) by extending a reported preparation of the corresponding benzoate. When tosyl chloride was warmed with tetrahydrofuran and zinc chloride, the temperature quickly shot up to 168 °C (efforts to temper this exotherm proved undesirable). When the reaction calmed down, further heating

then led to **108** in 46% yield (eqs. 40–41); incidentally, addition of K_2CO_3 in the distillation of **108** helped prevent autocatalytic decomposition.[124] The tosylate **108** did indeed alkylate a Grignard reagent (eq. 40), but the yield was only



27% (an accompanying reaction produced 1-bromo-4-chlorobutane in 52% yield).[124] Greater success can be forecast with other nucleophiles, nevertheless, because chloride and iodide ions as models gave the X-substituted products in yields of 54–60% (eq. 41).[124] An incidental (unrelated) entry into ester chemistry might be inserted here, i.e., synthesis of the benzenesulfonate of the highly hindered 2,4,6-tri-*t*-butylphenol.[125]

As for sulfonamides, we gave considerable attention to synthesis of 1,3-disulfonylureas (**109**, Scheme 21).[126] Our reason was that since both monoacyl- and diacylureas are pharmacologically active, known activity of monosulfonylureas seemed to call for testing of the disulfonylureas. As it turned out, the monosodium salts of **109** were diappointing as hypnotics, anticonvulsants, antitubercular, or chemotherapeutic agents.[126] Nevertheless, the new and general synthesis developed permitted bringing the informational status of the little known class of disulfonylureas at least a bit closer to that of the well-known monosulfonylureas. As Scheme 21 shows, the ureas **109** were



Scheme 21

produced by heating the salts of arene- and alkanesulfonamides with diphenyl carbonate and then acidifying;[126] for eight ureas of quite varied structure, yields were 57–89%.[126] The structures were confirmed by the independent synthesis of Scheme 21, as well as by neutralization equivalents and quantitative hydrolysis to sulfonamides and CO_2.[126]

As another incidental point, an inability reported by others of lithium aluminum hydride to reduce sulfonamides, in contrast to sulfonyl halides and anhydrides, seemed attributable to abstraction of an acidic hydrogen from the amide

to leave a refractory anion that would resist attack of a negative hydride ion.[123] Sure enough, *N,N*-diethylbenzenesulfonamide could be reduced, although such vigorous conditions were required that the benzenesulfinic acid produced (57% yield) was partially reduced to the thiol (10% yield).[123]

13.4. *Thiosulfonates*

13.4.1. *Preparation of Salts and Esters.* A convenient way to make thiosulfonate salts, such as **110**, is simply to heat a sulfinate salt with sulfur in alcoholic media (eq. 42); we found that a refinement of an old undetailed procedure of Otto works not only with an

$$RSO_2Na + S \xrightarrow{\Delta} RSO_2SNa \qquad (42)$$

110

arenesulfinate[100] but also (and far more rapidly) with an alkanesulfinate.[52] An interesting sulfur-grabbing reaction reminiscent of eq. 42 is the rearrangement of the trisulfide bissulfinate to the disulfide thiosulfonate shown earlier in eq. 25.[52]

We have prepared thiosulfonate esters in many ways. A chief way has been by oxidizing disulfides, with H_2O_2 as a chief agent; thiols of course also can be used since H_2O_2 rapidly oxidizes them to disulfides.[127] Christiansen and Dolliver patented the oxidation of cystamine dihydrochloride (**111**) with H_2O_2 (eq. 43), although like many

$$[Cl^-H_3N^+(CH_2)_2S]_2 + H_2O_2 \longrightarrow Cl^-H_3N^+(CH_2)_2SO_2S(CH_2)_2NH_3^+Cl^- \qquad (43)$$

111 **112**

before them they believed the products of such oxidations to be α-disulfoxides, RS(O)S(O)R (cf. refs. 31 and 127).[128] Others established the thiosulfonate structure for unsymmetrical disulfide dioxides, however, and Crenshaw and Owen did so in our laboratory with ^{35}S for a symmetrical one.[129] Consistent with the conclusions of thiosulfonate rather than α-disulfoxide structures, we have used the symmetrical amino thiosulfonate **112** and its *N,N'*-diacetyl derivative to convert thiols to the many aminoalkyl disulfides in Tables 1–3 (by eq. 10), and we developed a procedure for the routine preparation of **112** from the thiol for such purposes.[130] Aqueous H_2O_2 proved much the best oxidant of many tried for making the *N,N'*-diacetyl derivative of **112**.[31] It is interesting that the only unsymmetrical thiosulfonate we could isolate from the oxidation of aminoalkyl *t*-butyl disulfide salts had the two oxygens on the sulfur nearest the *t*-butyl group (isolation of **112** indicated some scrambling);[32] this result might stem from better electron supply there, which would fit with findings of Leandri and Tundo for unsymmetrical aryl disulfides. As mentioned in Sec. 5.3.1, the cyclic thiosulfon-

ates **31** with $n = 3$ or 4 were best obtained from the disulfides with H_2O_2-AcOH (although $NaBO_3$ was better for **31** with $n = 5$).[52] On the other hand, as related in Sec. 5.3.4, H_2O_2-AcOH put only one oxygen onto bis-(2,4,6-triisopropyl)phenyl disulfide, and the thiosulfinate then could not be easily oxidized to the thiosulfonate (**42**); ultimately, however, a witches' brew of H_2O_2-AcOH-WO_3-HCl-dioxane did give **42**.[67]

For alkyl alkanethiosulfonates, Douglass and Farah developed an ingenious and nearly quantitative synthesis by oxidation of dialkyl disulfides using a carefully gauged sequence of chlorinolysis in AcOH, followed by addition of H_2O (eq. 44).[131] For us, one convincing badge of merit for this reaction was that although H_2O_2 failed to oxidize

$$RSSR \xrightarrow{Cl_2,\ <0°C} \xrightarrow{AcOH} \xrightarrow{H_2O} RSO_2SR \tag{44}$$

di-2-(*n*-decylamino)ethyl disulfide dihydrochloride to the thiosulfonate, the Douglass-Farah reaction gave the thiosulfonate in 85% yield.[127] We later found that essentially the route of eq. 44 also gave excellent results in the synthesis of aryl arenethiosulfonates (R = Ar),[15,67] although bis-2,4,6-(triisopropyl)phenyl disulfide again misbehaved and was recovered unchanged.[67] Thiols sometimes may be easier to purify than disulfides and then are likely to be a better choice for the preparation of thiosulfonates.[16]

Still later, we found that sulfuryl chloride can replace Cl_2 in Douglass-Farah types of oxidations of disulfides or thiols to thiosulfonates;[132] the ease of handling,[132] and sometimes better yields,[17,132] point to it as a first choice. In some special oxidations to thiosulfonates, other agents proved useful; thus $NaBO_3$ worked better than KIO_4,[41] which in turn did better than *m*-chloroperoxybenzoic acid.[45]

Other useful preparations of thiosulfonates did not involve oxidation at all: the equilibration of a sulfinate salt and thiosulfonate, which depends on favorable solubilities (eq. 45);[118,133] reaction of a sulfonyl iodide and a silver thiolate (eq. 46);[30,118] reaction

$$RSO_2^- + R'SSO_2R' \rightleftharpoons RSO_2SR' + R'SO_2^- \tag{45}$$

$$RSO_2I + R'SAg \longrightarrow RSO_2SR' + AgI \tag{46}$$

$$2\,ArSO_2S^- + RX_2 \longrightarrow (ArSO_2S)_2R + 2X^- \tag{47}$$

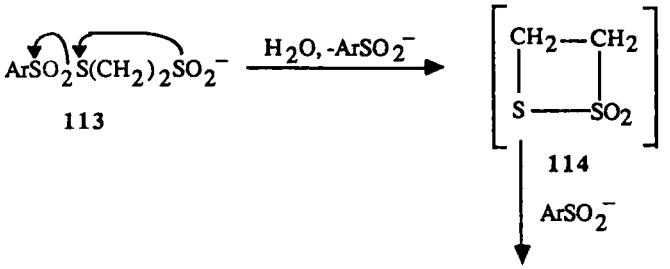
$$RSO_2^- + t\text{-BuSCl} \longrightarrow RSO_2S\text{-}t\text{-Bu} \tag{48}$$

of thiosulfonate salts with alkylene dihalides (eq. 47);[36] and the reaction of a thionitrite with a sulfinic acid (Scheme 11, **67**→**72**).[44] The method with thionitrites also was used with bifunctional sulfinic acids to make bisthiosulfonates of the structure RS-SO_2R'SO_2-SR, as was the method of eq. 45.[133] A final synthesis

was the reaction of a sulfinate salt and a sulfenyl halide; the tertiary alkyl thiosulfonate used as an illustration in eq. 48 was interesting both as representing a new class and showing low reactivity,[30] as had the sterically hindered triisopropylphenyl thiosulfinate mentioned earlier (Sec. 5.3.4) and its thiosulfonate (**42**).[30]

13.4.2. *Properties and Uses.* Prolonged storage is no problem with the aminoethyl thiosulfonate salt **112**, but the free base decomposes rapidly in water; almost no **112** is recovered when it is converted to the free base and then quickly back to **112**.[127] This instability, and that of other aminoalkyl thiosulfonate bases, is attributable to effects of the amino group, since the diacetyl derivative of **112** was recovered completely after two days in water.[127]

A quite interesting instance of instability was encountered with the thiosulfonate **113**, which results from interaction of a sulfinate-salt moiety (eq. 49).[100] Thus



113 114 (49)

$$ArSO_2(SCH_2CH_2SO_2)_nS(CH_2)_2SO_2Na$$

115

dissolution of **113** in water leads quickly to precipitation of a polymer (**115**), for which evidence was FAB^+ mass spectral peaks for each of the products from **115** having $n = 0$ through 5.[100] We attributed formation of **115** to a neighboring group effect of $—SO_2^-$, which produced the β-thiosultone **114**; an expelled arenesulfinate anion then initiated polymerization of **114** (eq. 49).[100] Support for such an effect was the relative stability of esters of **113**,[100] as well as the considerable stability of the sulfinyl thiosulfonate **116** inferable from the vigorous conditions of preparation (eq. 50).[66]

$$ArSO_2S^- + Cl(CH_2)_2\overset{O}{S}R \xrightarrow{60\text{-}80°C,\ 6h} ArSO_2S(CH_2)_2\overset{O}{S}R \qquad (50)$$

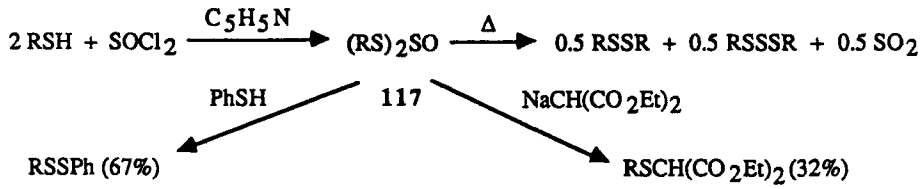
116

Uses of the thiosulfonate **6** were discussed in Sec. 2.2 (eq. 3). Uses of other thiosulfonates, also as thioalkylating agents, to prepare unsymmetrical disulfides were discussed in Sec. 5.1 for acyclic thiosulfonates (eq. 10), in Sec. 5.3.1 for cyclic thiosulfonates (eq. 19), and in Sec. 5.3.3 for sulfinyl thiosulfonates (eq. 20). In other work, bisthiosulfonates ($RSO_2—SR'S—O_2SR$, from eq. 47) were

used to prepare some of the bisdisulfides in Table 1 (cf. Entries 12, 27, 35),[36] and a number of aminoalkyl thiosulfonates were made available that can be used to make aminoalkyl disulfides.[127] Thiosulfonates may thioalkylate the thiol groups of people, too, and therefore they should be treated with reasonable respect (for example, an aminoalkyl thiosulfonate sometimes causes an annoying skin rash and contact with skin is best avoided).[130]

14. DERIVATIVES OF SULFUROUS AND SULFURIC ACID

Our major incursion into these areas was with dithiosulfites, $(RS)_2SO$.[134] Since our early efforts were hampered by instability of the initial dithiosulfites, we studied some decompositions as a start, so that we could predict the dithiosulfites most likely to be stable enough for convenient study. The *t*-butyl ester (**117**), prepared by modification of a method of Wolff (Scheme 22), was rather stable at 100 °C, but at 185 °C it decomposed quantitatively in less than an hour according to Scheme 22.[134]



Scheme 22. R = t-Bu.

Relative stabilities then were determined for a variety of dithiosulfites by decrease of the strong IR band for —S(O)— to half value. The following order of stability was found: *t*-alkyl >> aryl > *sec.*-alkyl >> primary alkyl (usually not soluble); half lives at 100 °C varied widely, from 0.25 h to about 48 h.[134] Several aryl dithiosulfites could be isolated, as could some unsymmetrical dithiosulfites of the structure *t*-BuSS(O)SR.[134] A kinetic study with diphenyl dithiosulfite showed that the decomposition, which produced diphenyl di- and trisulfide and SO_2,[134] was first order and strongly catalyzed by SO_2; the decomposition seemed to be heterolytic rather than homolytic.[134] Scrambling of groups occurred when two different dithiosulfites or an unsymmetrical dithiosulfite were used. Here, again, the reader is invited to compare a mechanism for the decomposition with one we suggested.[134]

As might be expected, the ester **117** resembled thiosulfonates and thiosulfinates in thioalkylating capabilities, as Scheme 22 illustrates.[134] Interestingly, di-*t*-butyl dithiosulfite (**117**) was quite resistant to air oxidation; efforts to oxidize **117** to the dithiosulfate either had no effect or totally destroyed it.[134]

Thiosulfates received a little attention in our work, in the form of Bunte salts. As discussed later, an interesting preparation was the cleavage of thiirane 1,1-

dioxide by sodium thiosulfate (eq. 52); the product, $NaO_3SS(CH_2)_2SO_2Na$, could be reduced to sodium 2-mercaptoethanesulfinate or converted with base to the disulfide, $[S(CH_2)_2SO_2Na]_2$.[100] Sulfuryl chloride converted an amino Bunte salt, $RNH_2^+(CH_2)_2SSO_3^-$ to a thiosulfonate, $RNH_2^+(CH_2)_2SO_2S(CH_2)_2NH_2^+R$; this Bunte salt thus behaved like the disulfides or thiols mentioned in Sec. 13.4.1.[132] Another Bunte salt, **118**, prepared as shown in eq. 51, thioalkylated a thiol (eq. 51), but an effort to thioalkylate NaSH twice in

$$\underset{R = AcNH(CH_2)_2.}{RSSR} \xrightarrow{Na_2SO_3,\ NH_4OH,\ CuSO_4} \underset{\mathbf{118}}{RSSO_3Na} \xrightarrow{RSH} RSSR \qquad (51)$$

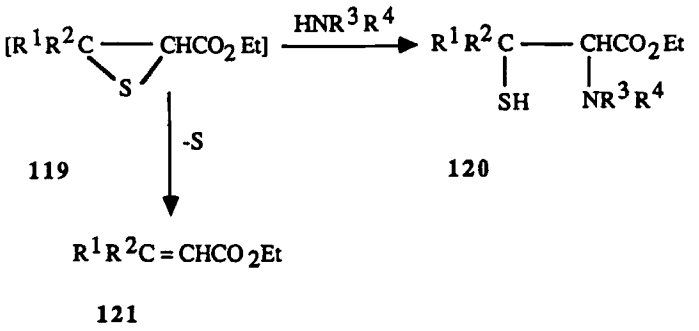
this way to give a trisulfide gave no pure trisulfide (although chromatography did indicate modest formation).[70]

With esters of sulfuric acid, our principal encounter was in using dialkyl sulfates as alkylating agents, e.g. to convert sulfinate salts to sulfones.[112,113]

15. HETEROCYCLES

15.1. *Three- through Six-membered Rings*

Our initial entry into the chemistry of small-ring sulfur-containing heterocyles was prompted by the hope that α,β-epithio esters, such as **119**, could be cleaved to give substituted cysteines, such as **120** (Scheme 23), which were potential antiradiation drugs.

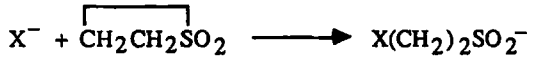


Scheme 23

At that time, the first α,β-epithio ester had been reported, by Durden and coworkers (**119**, with R^1 = Me, R^2 = Et),[135] but with Dr. Durden's cooperation we found that this product actually was a β,γ-epithio ester.[136,137] We were unable to synthesize α,β-epithio esters either with R^1 = H, R^2 = Alk, or R^1 = R^2 = Alk, although isolation of **121** in low yield may have indicated that **119** formed

but then lost sulfur to give **121** (with R^1 = Me, R^2 = Et).[136,138] With one aromatic substituent, conventional thiirane syntheses also gave unsaturated esters, in up to 80% yield (**121**, R^1 = H, R^2 = Ph), but still no α,β-epithio esters.[139] Aside from unsaturated esters, the main products with alkyl or aryl types were α-mercaptoacrylates, hydrolysis products, and dimers or polymers.[136,139] Efforts to synthesize **119** with R^1 = R^2 = Ph either by conventional means or by a Darzens-type condensation of thiobenzophenone with ethyl chloroacetate also came no closer than the unsaturated ester (**121**, R^1 = R^2 = Ph).[139]

Possible involvement of three-membered rings containing phosphorus, sulfur, and oxygen in oxidation of thionophosphorus compounds was discussed in Sec. 9.2. In other work on three-membered rings, X-ray analysis of a camphor-based thiirane 1,1-dioxide derivative confirmed the nature of ring opening by a thiolate,[102] and we found that thiirane 1,1-dioxide (**122**) afforded an excellent avenue to a wide variety of 2-substituted ethanesulfinates we desired for biological studies (eq. 52).[100] Products from eq. 52 are useful precursors of disulfides, trisulfides, and sulfinic esters.[100]

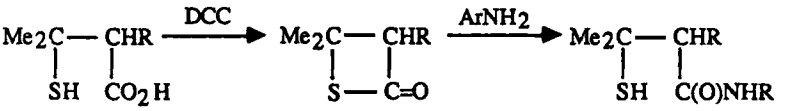


(52)

122

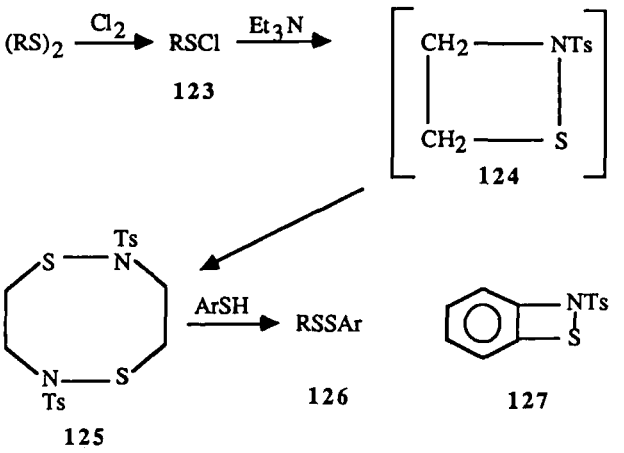
X = HS, AlkS, ArS, $ArSO_2S$, Li_2O_3PS and SSO_3 Na.

A transitory four-membered thiosultone (**114**) was an interesting probability in the reaction of one product from eq. 52 (**113**, in eq. 49).[100] Another brief entry into four-membered ring chemistry came in the use of *N*,*N*′-dicyclohexylcarbodiimide (DCC) to prepare the amide shown in eq. 53, based on work of Sheehan and Pollak (cf. ref. 77),



(53)

along with some related work on the solvolysis and polymerization of some α-amino β-thiolactone derivatives.[140] Effort with four-membered rings also was applied to thiazetidines such as **124** and thiazetes such as **127** (Scheme 24).[141] After the reaction of **123** in Scheme 24, mass spectra revealed the presence only of the dimer **125**, with no indication of **124**.[141] Analysis of **125** by titration with a thiol (which gave **126**) indicated



Scheme 24. R = p-$MeC_6H_4SO_2NH(CH_2)_2$; Ts = p-$MeC_6H_4SO_2$

that the dimer **125** had formed in quantitative yield.[141] This product (**125**) had properties consistent with structure **125** but not with alternatives (reduction to a thiol, spectra, oxidation of I^- to I_2).[141] Although **125** could have been formed of course by direct reaction of two molecules of **123**, there was reason to invoke **124** as an intermediate.[141] Attempts to synthesize **127** led mainly to polymer.[141]

Five-membered thiazolidines were discussed in Sec. 4 and five- to seven-membered cyclic disulfides in Sec. 5.3.

15.2. *Seven- and Eight-membered Rings*

The seven-membered ring 1,2,5-trithiepane (**128**) was synthesized to permit examination of a sulfide and disulfide moiety in close proximity (eq. 54).[142] Since our product was

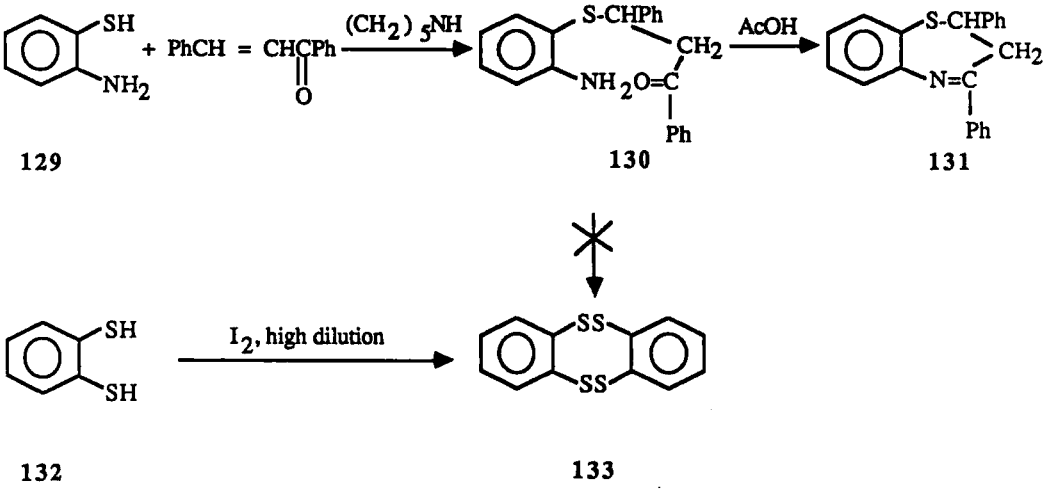
$$HS(CH_2)_2S(CH_2)_2SH \xrightarrow{FeCl_3} \overbrace{S(CH_2)_2S(CH_2)_2S} \qquad (54)$$

128

quite different from three reported earlier to be **128**, the structure was confirmed with special care (NMR, Raman, UV, and mass spectra; molecular weight).[142] Formation at the sulfide sulfur of a sulfoxide and a sulfonium salt showed selective reaction of a sulfide to be possible in the presence of a disulfide.[142] Comparison of the reactivity and spectra of **128**, the sulfonium salt, the sulfoxide,

and the seven-membered disulfide 1,2-dithiepane showed there were no marked interactions of the disulfide function with any of the others;[142] this point is biologically relevant since the disulfide and the other functions can almost touch in models, as they might in proteins.[142] In connection with this work, the chemistry of monocyclic seven-membered rings with one to seven sulfur atoms was reviewed.[143]

The eight-membered ring, "bis(*o*-phenylene) tetrasulfide" (**133**, Scheme 25) was of interest as a prototype of a class for several reasons: the possibility of *syn/anti* forms where the benzene rings could be on the same or opposite sides of the plane of sulfur atoms; the possibility of ring-ring interactions of the *syn* form; the effects of the electron swarms around the sulfur atoms; and, isosteric effects resulting from similarities of a sulfur atom and a carbon-carbon double bond (cf. thiophene and benzene).[144] One approach to



Scheme 25

the synthesis of **133** was to protect *o*-aminobenzenethiol (**129**) as **130** (by a method like one of Herz and Tarbell),[80] then to convert **130** to a disulfide by diazotization and treatment with Na_2S_2, and finally to deprotect and ring-close the resulting dithiol (Scheme 25). The ketone **130** was obtained,[80] but it could not be converted to **133**; an interesting byway, however, was cyclization of **130** to the seven-membered **131**.[80]

We finally obtained **133** by high-dilution oxidation of the dithiol **132** (Scheme 25).[144] The tetrasulfide **133** was intriguing in its similarity to sulfur, e.g. in its lemon-yellow color and its polymerization when heated (although it is quite stable at ca. 25 °C).[144] At this point other interests compellingly supervened, so that we never got around to further pursuit of our initial objectives; we hope

others will take up the promising and interesting possibilities related to the class of which **133** is the prototype.

16. BIOLOGICAL ASPECTS

16.1. *Antimicrobial Agents*

The fact that many thiocarboxylates and dithiocarbamates had been reported to show significant antimicrobial action led us to test a number of acyl and thiocarbamyl unsymmetrical disulfides.[145] Since several were promising against bacteria and, particularly, fungi,[145] we began a collaboration with a colleague at VU, Prof. Ilda McVeigh, an expert of long standing on the disease histoplasmosis. Histoplasmosis is caused by the fungus *Histoplasma capsulatum*, which has received increasing diagnosis and recognition as a dangerous pathogen; it is widespread in some areas and has been estimated to cause at least 800 deaths annually.[146] Table 4 summarizes some of the activities we shall discuss, in comparison with amphotericin, a standard but undesirably toxic drug.

In vitro screening against *H. capsulatum* revealed promise for several classes: disulfides, thiols, thiocyanates, thio acids, and thiosulfonates (cf. Table 4, respectively Entries 2–4, 5, 6, 7 and 8). A number of carbonyl disulfides were prepared and tested [i.e. RC(O)SSR']; those with short unbranched alkyl chains or unsubstituted aryl groups seemed best *in vitro*, but of these only acetyl methyl disulfide showed statistically significant activity *in vivo* in mice (Table 4, Entry 11).[21] Further elaboration was presented on our work to this point, along with new information, e.g. on 2-(*n*-decylamino)ethyl disulfides (cf. Table 4, Entry 4).[147] Of several acetyl β-substituted ethyl disulfides prepared in order to follow up the promise of acetyl methyl disulfide (Table 4, Entry 11), three showed statistically significant activity *in vivo* (Table 4, Entry 12).

At this point, the *in vitro* activities of 77 of our disulfides were subjected to linear regression analysis by the Free-Wilson approach; substituent constants were determined for 53 groups with the hope that optimum structures could be predicted for subsequent synthesis.[150] We predicted the following groups to be best:[150] morpholino (cf. Table 4, Entry 9), *p*-tolyl (cf. Table 4, Entries 2 and 4), and dimethylamino (cf. Table 4, Entries 2 and 10), along with phenyl and 2-chloroethyl. Of 15 disulfides we then prepared, about half were active *in vitro*, although lamentably none was significantly active *in vivo*; all compounds found active were predicted to be, although not all compounds predicted to be active actually proved to be active.[42]

Table 4 shows some of the better compounds. Even though *in vivo* activities were relatively low, perhaps because of improper tissue distribution or premature destruction (e.g. by the liver), along with leads for histoplasmosis readers may infer worthwhile leads to topical or agricultural fungicides. Other aspects also seem worth following up. For example, prototypes such as the first seven in Table 4 never were tested *in vivo* (i.e. Entries 2–8). Moreover, modification of features such as steric hindrance and functionality might obviate destruction and lead to useful *in vivo* activity against histoplasmosis.

TABLE 4. Activities against *Histoplasma capsulatum*

Entry	Name or structure of compound	*In vitro*, minimum inhibitory conc'n., μg/mL[a]	*In vivo*, extension or survival, %[b]	Ref.
1	Amphotericin B[c]	0.1[21]	31–108[d,24,42]	
2	$Me_2NC(S)SS$-*p*-MeC_6H_4	≤1		147
3	$Me_2NC(S)SS$-*o*-$HO_2CC_6H_4$	<1		42
4	*p*-$MeC_6H_4CH_2SS(CH_2)_2NH$-*n*-$C_{10}H_{21}\cdot HCl$	2.5		147
5	*p*-ClC_6H_4SH	2.5		147, 148
6	$CH_2(SCN)_2$	2.5		149
7	$CH_3CH_2C(O)SH$	10		148
8	$MeSSO_2Me$	10		148
9	$O(CH_2CH_2)_2NC(S)SS(CH_2)_4SO_2Na$	1	18	24
10	$Me_2NC(S)SS$-*p*-ClC_6H_4	5	13	42
11	AcSSMe	8	17	21
12	$AcSS(CH_2)_{2\text{-}4}CO_2H$	>20	14	25

[a]Best result with either the H-7 or H-25 strain of *H. capsulatum*.

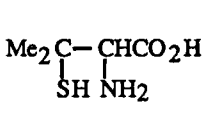
[b]Best result, kindly provided through the Eli Lilly Co., as per cent prolongation beyond controls of mouse life after exposure to X-rays, then infection with *H. capsulatum*, then administration of agent.[21]

[c]Standard drug, but undesirably toxic.

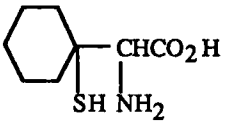
[d]At 12.5–50 mg/kg.

16.2. *Antiarthritic Agents*

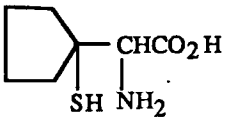
Rheumatoid arthritis affects millions of people and costs billions of dollars annually, but even now the cause(s) of the disease are unclear, and most palliative drugs strike only at the symptoms. I. A. Jaffe had found that D-penicillamine (**D-5**) effects significant improvement in arthritic patients, although it can lead to serious side effects; the D-enantiomer is used because the L-enantiomer inhibits Vitamin B-6 and is more toxic (cf. ref. 151). We undertook collaboration with Dr. Jaffe in the hope of learning the



5



134



135

requirements for the functional groups and skeleton for such activity of (**D**) − **5**, of developing syntheses that could make improvements possible, and of gaining insight into the mechanism of action.[151]

One means of assessing antiarthritic activity is after inducing "adjuvant arthritis" in animals, but this was no help because (**D**) − **5** proved to be essentially inactive.[151] Since there was no other promising means of testing directly for antiarthritic activity of counterparts of (**D**) − **5**, our best assessment seemed to lie in measuring the skin tensile strength ("STS") of rats after the counterparts of **5** had been fed in the diet for 14 days.[151] This approach was based on the finding of M. E. Nimni that (**D**) − **5** caused a marked decrease in STS; it seemed a reasonable way to go since arthritis is a disease of connective tissue and since Nimni had shown that (**D**) − **5** owed its effect on STS to interaction with collagen, which is a principal protein of connective tissue (cf. refs. 151 and 154 for references). Even if skin tensile studies proved to be unrelated to arthritis, however, they seemed likely to be worthwhile both for basic biochemical significance and relevance to side effects in the use of (**D**) − **5** for a wide variety of diseases beside arthritis (e.g. Wilson's Disease, cystinuria, scleroderma).[151]

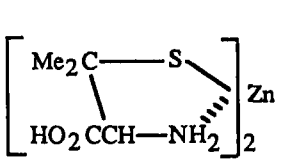
Trial of numerous compounds showed that SH, NH_2, and CO_2H all were necessary for reduction of STS, since activity was lost when any one of them was absent or blocked.[140,151] The methyl groups of **5** could be made part of a ring, as in **134**[151] and **135**,[140] but one methyl group could neither be dispensed with[140] nor replaced by ethyl.[151] It might be added that although (**D**) − **5** is used with patients because of the anti-Vitamin B_6 effect of (**L**) − **5**, optical activity is unnecessary for STS effects.[140,151,154]

After an interim report,[152] continued work confirmed and extended our earlier conclusions.[140] Additionally, a polymer of (**D**) − **5** was prepared from the thiolactone shown in eq. 53, where R was $NH_3^+Br^-$, by simply adding one equivalent

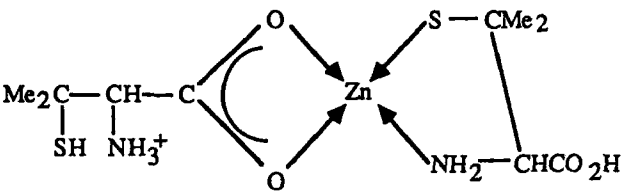
amount of base to an aqueous solution of the salt; the resulting α-amino-β-thiolactone homopolymerized to polymers with molecular weights of ca. 1200 Daltons. It is interesting that reaction at high dilution, on the other hand, gave only (**D**) − **5** and no polymer, presumably because an intramolecular neighboring-group (NH_2)-assisted solvolysis predominated.[140] A typical polymer had no effect on STS, probably because rats couldn't hydrolyze it readily.[140]

Of considerable interest to us was the analog of **5** in which each methyl group was trifluorinated.[81] Although some interesting fluorine chemistry developed, we did not succeed in synthesizing this hexafluoropenicillamine.[81]

A zinc chelate of (**D**) − **5** attracted our attention in part because of an influence reported of (**D**) − **5** on the zinc balance of patients, but even more because a report that zinc accumulates in inflamed joints indicated that a zinc chelate might deliver (**D**) − **5** selectively to arthritic joints (cf. ref. 140). Studies of the zinc chelate *in solution* by several groups had pointed to **136** as the structure (cf. ref. 140). We isolated a solid product, for the first



136



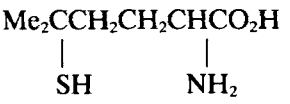
137

time, which several kinds of evidence indicated to be a 2:1 chelate of (**D**) − **5** with zinc.[140] Our conclusion from X-ray photoelectron spectroscopy was that the structure of the *solid* was **137**, at least at the surface, although we felt that this product might well exist as **136** *in solution*.[153] The effect of this isolated chelate on STS was about the same as that of (**D,L**) − **5**; apparently the activity did not depend on hydrolysis to (**D**) − **5** in the stomach, since the chelate was active by intraperitoneal (ip) injection.[154] Here, I should add that we had hoped we could change to the ip route for administering agents in STS tests, instead of by using feeding in the diet, not only because of the waste in feeding and the difficulty of using liquids, but also because the ip route would avoid gastrointestinal complications (hydrolysis, irritation, etc.), as well as too low a consumption of agent because of loss of appetite;[154] despite some apprehension beforehand as to complicating effects of shock, the ip route succeeded;[140,154] two compounds, as well as the zinc chelate, which had reduced STS orally did so by the ip route as well and gave suitable dose-response relations.[154]

The zinc chelate proved to be rather toxic by the ip route.[154] Since oral zinc sulfate had been suggested for use in rheumatoid arthritis by others, after confirming the parenteral toxicity of our chelate,[155] we cautioned that clinical study of (**D**) − **5** with oral zinc supplements should be contemplated only with great circumspection because of the possible toxic hazard.[154,155]

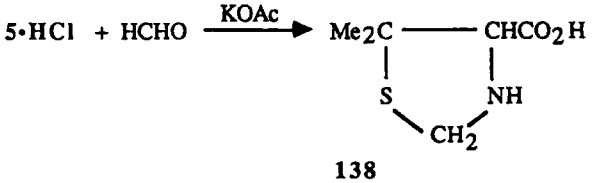
Jaffe had concluded that chelation effects seemed unlikely to explain the activity of **(D) − 5** in arthritis (cf. ref. 151), although we later obtained evidence that such activity indeed might result from a two-fold effect of **(D) − 5**, viz. conversion of both inflammagenic circulating Cu(II) and inert (protein-bound) Cu(II) to anti-inflammatory copper complexes.[156]

The activity of **(D) − 5** in arthritis and/or in other diseases thus might be a consequence of good chelating capability (cf. ref. 9), which would depend on formation of a five-membered ring such as those of **136** or **137**. However, alternatively, since formation of a five-membered ring (a thiazolidine) evidently is responsible for the reduction of STS by **(D) − 5** (through formation of thiazolidines with aldehyde groups of collagen required for crosslinking; cf. ref. 154), antiarthritic activity might result from such an interference with collagen biochemistry. Either chelation or thiazolidine formation should be much diminished with the bishomolog of penicillamine mentioned earlier (**4**, $n = 2$) as a probe, relative to **5** itself, since less readily formed seven-membered rings would be required. On the other hand, if only independent action of SH and NH_2 were involved in a particular biological activity, **4** ($n = 2$) should be as effective as **5** when substituted for it. Compound **4** ($n = 2$) was synthesized to permit such comparison.[9] As expected, **4** ($n = 2$) did indeed



4, $n = 2$

react much less readily with formaldehyde under conditions where **5·HCl** gave the thiazolidine **138** in 79% yield (eq. 55).[9] It also coordinated less readily with Fe(III) or



(55)

138

Cu(II) than did **5**.[9] We hope that substitution of **4** ($n = 2$) for **5** in biological situations will enable one to ascertain whether the SH and NH_2 groups of **5** are important in the situation because of five-membered ring formation or because of action as independent functional groups (cf. ref. 157 for one such use).

Several explanations for the activity of **D-5** in arthritis have been considered: (1,2) As mentioned, chelation effects and/or inhibition of collagen crosslinking may be involved. (3) Since **(D) − 5** inhibits bone formation, this feature may play a role (some of our analogs were even more effective).[157] (4) Opinion seems

to be leaning toward the view that rheumatoid arthritis is an autoimmune disease, in which a malfunctioning immune system damages the tissues involved. Although immunosuppressive drugs have become of considerable interest for arthritis, we reported that **(D) − 5** shows only low immunosuppressive activity in certain types of mouse assays, in common with other reports of little or no immunosuppressive activity.[151] Notwithstanding, we were able to report later that in at least one immunochemical reaction **(D) − 5** inhibits some aspects of the functions of T- and B-type lymphocytes and to suggest that its effects on cellular immunity warranted further consideration.[158] (5) Jaffe concluded that dissociation of the "rheumatoid factor" (a protein frequently present in the blood in arthritis), perhaps by thiol-disulfide interchange, was an improbable explanation for activity, and our work was in accordance, although we confirmed that such dissociations can occur.[151] (6) Since **(D) − 5** showed little anti-inflammatory action, such as that of aspirin and other nonsteroidal drugs, anti-inflammatory action probably plays no significant role.[151] (7) Chloroquine and cortisone may act by stabilizing membranes of lysosomes (inside cells), disruption of which leads to release of damaging enzymes. At least with liver lysosomes, however, **(D) − 5** had no stabilizing effect.[151]

Our efforts to develop new analyses for the plasma level of **(D) − 5** in patients led to the thionitrite research described in Sec. 7.2.[78] The thionitrite of **(D) − 5** gave a nice green solution that followed Beer's Law, but unfortunately concentrations could be determined only above 5 mM (± 20%) and reliably only at 20 mM (± 0%),[78] which is too high for an estimated maximum concentration of ca. 1.7 mM for **(D) = 5** in patients.[158]

Our analytical effort also led to synthesis of some more unsymmetrical tertiary disulfides (cf. Sec. 5).[44] In particular, the reaction of eq. 56 (an application of eq. 13) was used with *N*-acetylpenicillamine (as RSH) to obtain **140**. The disulfide **140** was desired as a model to test the feasibility of using eq. 56 for fluorimetric analyses of **5** and

$$\underset{\text{Cl}^-}{\text{RSH} + 5\text{-Me}_2\text{N}^+\text{C}_{10}\text{H}_6\text{-1-SSCO}_2\text{Me}} \longrightarrow \underset{\text{Cl}^-}{5\text{-Me}_2\text{N}^+\text{C}_{10}\text{H}_6\text{-1-SSR}} + \text{COS} + \text{MeOH} \quad (56)$$

139 **140**

$\text{R} = \text{CMe}_2\text{CH(NHAc)CO}_2\text{H}$; C_{10}H_6 = naphthyl.

its derivatives, since the naphthalenethiol corresponding to **139** fluoresced comparably to dansyl chloride (the corresponding sulfonyl chloride, a well known reagent used as a fluorescent label for amino acids and proteins).[44] Fluorescence spectra of **139** and **140** indicated, however, that such disulfides probably would fluoresce too weakly for the spectra to be analytically useful;[44] we concluded that the disulfide linkage damped the desired fluorescence by acting as an "energy sink."[44]

We made another approach to arthritis quite different from that with penicillamine, in collaboration with Michael Whitehouse and Frances Beck.[159] White-

house and his associates had developed strong evidence that lymphocyte cells play an important role in rheumatoid arthritis and that "gagging" such lymphocytes might provide a means of controlling rheumatoid arthritis and certain autointolerant disorders.[159] Whitehouse invented the neologism "ZOG" for agents that could effect such blocking (from *Zello*berflächen*gi*fte, the German for cell-surface poison).[159] The idea of a ZOG is that it should affect only crucial *external* receptor sites of lymphocytes, because of being too polar to penetrate into the *interior* of cells and interfere there with normal cellular processes.[159] We thought that several dozen of our compounds might be prospects as ZOG's, for blocking SH groups as recognition sites on lymphocytes while being too polar to penetrate into the cell.[159] Of these, assessment by an immunological means (graft-versus-host reaction) showed that eight disulfides and one thiosulfonate indeed were promising as ZOG's. The capability of disulfides and thiosulfonates for thioalkylation of SH led us to attribute the activity found as ZOG's to replacement of the H of SH in cell-surface thiol receptors (cf. eqs. 10 and 13, and refs. 29 and 159). It seems more than coincidental that all but one of our ZOG's contained —$NH(CH_2)_2S$— groups (although so did many of our inactive compounds).[159] The results seem well worth following up "vis-à-vis potential applications as immunological probes and blocking agents, as well as therapeutic agents."[159]

16.3. *Antiradiation Agents*

Some thirty years ago, Dr. David Jacobus and Dr. Thomas Sweeney of the Walter Reed Army Institute of Research (WRAIR) contacted me as to possible interest in developing drugs for protection against ionizing radiation. There seemed to be a good prospect for combining useful organic chemistry with interesting medicinal chemistry, and the outcome was research at VU that began in 1959 and continued off and on until I retired in 1989. An attraction of research with "antirads" lay not only in such matters nuclear as protection of reactor and military personnel and industrial materials but, as a review describes,[160] also in potentials for protection against solar flares in manned space flight and for diminishing side effects in cancer therapy. Furthermore, radiation never develops the resistance to useful agents that can make antibiotics and pesticides obsolete! Dr. Sweeney, in an admirable compendium, summarized and analyzed structure-activity relationships for the 4400 compounds synthesized through 1973 by the numerous participants in the WRAIR program, which was supported by the U.S. Army Medical Research and Development Command[161] (as will be seen, quite a few of our better agents were made during still later programs developed by WRAIR).

Table 5 summarizes the most active classes that came from our research, and Table 6 illustrates tempting but unpromising extensions that others can be spared from trying. In Table 5, superscripts cite references to our syntheses, and page references to Sweeney's compendium give the location of biological details (where free acids or bases are listed rather than the salts actually tested).[161]

TABLE 5. Antiradiation Drugs That Led to Survival of 50–100% of Mice[a]

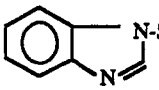
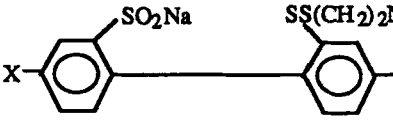
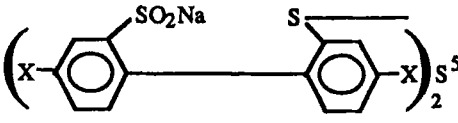
Entry	Structure, with reference for synthesis[b]	Dose, mg/kg[c]	Rating[d]	Ref. 161, page[e]
1	$H_2N(CH_2)_2SO_2S(CH_2)_2NH_2 \cdot 2\ HCl$, **112**[31,130]	500	±,+,o*	54
2	$AcNH(CH_2)_2SO_2S(CH_2)_2NHAc$[31]	750	+,o	209
3	$n\text{-}C_{10}H_{21}NH(CH_2)_2SO_2S(CH_2)_2NH\text{-}n\text{-}C_{10}H_{21} \cdot 2\ HCl$[127]	15	+,±	631
4	$n\text{-}C_{10}H_{21}NH(CH_2)_2SS(CH_2)_3NHAc \cdot HCl$[38]	56	+,±	581
5	$2\text{-}HO_2CC_6H_4SS(CH_2)_2NH_2$[15]	225	+,±	237
6	$2\text{-}HO_3SC_6H_4SS(CH_2)_2NH_2$[16]	600	+,±	189
7	$t\text{-}BuSSC(S)NR^1R^2$[23], $R^1 = R^2$ = H or Me	500-560	+	75,166
8	$F_3CCH(OH)S(CH_2)_2NH_2 \cdot HCl$[13]	320	+,+,o	37
9	$(EtO_2C)_2C(SCH_2CH_2NH_2)_2 \cdot 2\ HCl$, **15**[28]	150	+,o*	360
10		200	±,o*	332
11	$AcNH(CH_2)_2SS(CH_2)_4SO_2Na$ (**141**)[54]	370	+,+,+, +,+,o*	214
12	$HS(CH_2)_4SO_2Na$[72]	1200	+,±,±,±	(162)[f]
13	*cis*- or *trans*-$CH_2NAcCH(CO_2Me)CH_2CH\text{-}SS(CH_2)_4S(O)OMe$[55]	300	+,+,±	(162)[f]
14	$AcNH(CH_2)_2SSCH_2C_6H_4\text{-}2\text{-}CH_2SO_2Na$[45]	300	+,+,+,±*	385
15	$RSS(CH_2)_4SO_2Na$, R = $4\text{-}CH_3C_6H_4$[42]	63	+,+,+	(162)[f]
16	$NaO_2S(CH_2)_4SS(CH_2)_4SO_2Na$[50]	400	o,+	769
17	$NaO_2S(CH_2)_4SSS(CH_2)_4SO_2Na$[50]	300	+,+,+, +,±,o*	221, 769
18	$(2\text{-}NaO_2SCH_2C_6H_4CH_2S)_2S$[45]	446	+,+,+,±*	547
19	$NaO_2S(CH_2)_4SSSSS(CH_2)_4SO_2Na$[72,73] (**51**, with ■ = 4, m = 4-5)	134	+,+,o	(162)[f]
20		80-100[g]	+[g]	544, 546
21		40[h]	o,+,+,+ o[h]*	625,624, 769

TABLE 5 (continued)

Entry	Structure, with reference for synthesis[b]	Dose, mg/kg[c]	Rating[d]	Ref. 161, page[e]
22	n-$C_4H_9SS(CH_2)_4SO_2Na$[51]	150	+,o	(163)[f]
23	$NaO_2S(CH_2)_4SS(CH_2)_nSS(CH_2)_4SO_2Na$, n = 4[37,164]	600	+,+,±,±	(162)[f]
24	$HO_2C(CH_2)_2SS(CH_2)_nSO_2Na$, n = 4[37,165]	75	+,o	(162)[f]
25	$HOCH_2CH(OH)CH_2SS(CH_2)_4SO_2Na$[37,166]	600	+,+,+,o,±*	(163)[f]
26	$PhCH_2S(O)(CH_2)_2SS(CH_2)_4SS(CH_2)S(O)CH_2$h[66]	600	±,o	(163)[f]

[a] The % of a group of mice that survived for 30 days when given the intraperitoneal (ip) dose shown, calculated as the non-salt form, of the drug before irradiation. The level of radiation used led to 0% survival of controls.

[b] Superscripts by structures show present reference numbers for syntheses.

[c] Usually administered 15-30 min before mice were exposed to otherwise lethal irradiation from X-ray or ^{60}Co. Dose is that calculated for the free acid or base corresponding to the salt actually used.

[d] Ratings are those assigned by T. R. Sweeney in ref. 161, i.e. + = 50-100% survival, ± = 20-49% survival, and o = 0-19% survival. Successive symbols show the response at 1/2 the immediately preceding dose. An asterisk (*) signifies the drug led to at least 20-49% survival (i.e. ±) when given orally (po; dose not specified). Since ref. 161 covers only through 1973, biological data in our later papers are recast into the form used in ref. 161. Activities in ref. 161 are final values and are more dependable than earlier ones in our papers.

[e] Page number for the compound in ref. 161. The compound can be located readily among the relatively few on each page.

[f] Synthesized and tested after appearance of ref. 161. See the parenthesized reference for biological data, which have been recast into the form of ref. 161.

[g] Range is given for X = H or Cl.

[h] For X = H. With X = Cl, the compound was active ip and po but was less promising.

So far as we know, our reports of radioprotective activity were the first for the seven different classes in Table 5. Included are the classes of thiosulfonates (Entries 1–3), unsymmetrical amino disulfides (Entries 4–6) and thiocarbamyl disulfides (Entry 7), hemithioacetals (Entry 8) and thioketals (Entry 9), sulfenamides (Entry 10), and (especially) disulfide-sulfinic acids and congeners (Entries 11–26). Entries 15–26 excited special interest because (except for Entry 20) unlike most antiradiation drugs they contain no nitrogen (cf. ref. 160 and p. 5 of ref. 161).

Biological testing was arranged by WRAIR and involved determination of the toxicity of a drug and then administration at about two thirds or less of the toxic dose to a group of mice. After 15–30 min, the mice then were exposed to a level of radiation from X-ray or ^{60}Co that would be lethal to all unprotected controls. If 50% or more of the drugged group survived for 30 days, the agent was considered good (+), and if 20–49% survived it was considered fair (±). In the

TABLE 6. Representative Unpromising Antiradiation Candidates[a]

Structure, and ref. for synthesis[b]	Page(s) in ref. 161	Structure, and ref. for synthesis[b]	Page(s) in ref. 161
		Thiosulfonates	
$R^1R^2NH(CH_2)_2SO_2S(CH_2)_2$-$NHR^1R^2 \cdot 2\ HCl$[#,127]	131, 226, 428	$ArSO_2SR$[30,67,118]	338, 344 373
t-$BuSO_2S(CH_2)_2NH_2 \cdot HCl$[32]	125	$[AcNH(CH_2)_2SSO_2(CH_2)_2]_2$[133]	420
$H_2N(CH_2)_5SO_2S(CH_2)_5$-$NH_2 \cdot 2\ HCl$[127]	320	*trans*-$SCH_2CH(OAc)CH(OAc)$-CH_2SO_2[#,59]	195
		Disulfides	
$ArCH_2SS(CH_2)_2NH$-*n*-$C_{10}H_{21} \cdot HCl$[#,47]	603, 604 611, 612	$AcNH(CH_2)_2SS(CH_2)_2NHAc$[31]	207
Alk or $ArSS(CH_2)_2NH_2 \cdot HCl$[31,32,34]	129, 190, 242, 245, 578	$Ar[SS(CH_2)_2NH_2]_2 \cdot 2\ HCl$[7,35]	297, 351 381
$RSS(CH_2)_2NHAc$[#,22,35,38]	306, 330, 566	$AlkC(O)SSR$[#,21,22]	22, 100, 180, 235, 335
$HO_2C(CH_2)_{1-4}SS(CH_2)_2$-$NHAc$[#,33]	100, 152, 204,[c] 255		

	Dithiocarbamates and Trithiopercarbamates		
$Me_2NC(S)SS(CH_2)_4SO_2Na$[24]	161	$(CH_2)_5NC(S)SR$[64]	412, 561
$O(CH_2CH_2)_2NC(S)SS(CH_2)_2$-$NHAc$[#,79]	252	$H_2N(CH_2)_2NHC(S)SR\cdot HCl$[64]	287
	Disulfide-sulfinic Acids and Congeners		
$RSS(CH_2)_4SO_2Na$[162,163]	d	$H_2N(CH_2)_2SS(CH_2)_4SO_2CH_2$-$Ph\cdot HCl$[#,54]	452, 529
$AcNH(CH_2)_2SS(CH_2)_4$-SO_3Na[#,54]	214	$AcNH(CH_2)_2SSCH_2CH(OAc)$-$CH(OAc)CH_2SO_2Na$[59]	408
	Trisulfide-sulfinic Acids		
$[NaO_2SCH_2CH(OAc)CH$-$(OAc)CH_2S]_2S$[45]	558	$[1\text{-}NaO_2SC_{10}H_6\text{-}8\text{-}S]_2S$[#,53]	605
	Miscellaneous		
$[AcNH(CH_2)_2S]_2S$[70]	208	$AcNH(CH_2)_2SCH(CO_2H)$-CH_2CO_2H[14]	196
$NaO_2C(CH_2)_2SO_2Na$[162]	d	$NaO_3SS(CH_2)_2SO_2Na$[163]	d
$ArCH_2S(O)(CH_2)_2SSR$[163]	d	$Li_2O_3PS(CH_2)_2SO_2Li$[163]	d
$AcNH(CH_2)_2SCHPhCH_2$-$CONHAr$[#,14]	598		

[a]The 30-day survival of treated mice was less than 50%. Structures where at least one representative had at least fair activity (i.e., ±, corresponding to 20–49% survival) are indicated by #; the activity of all other agents was 0–19%. Ref. 161 gives details of toxicity and activity. Some other unpromising leads are mentioned in the text.

[b]Superscripts by structures show present reference numbers for syntheses.

[c]In ref. 161, p. 204, for $\cdots SS(CH_2)_2CO_2H$, read $\cdots SS(CH_2)_3CO_2H$.

[d]Research done after the compilations of ref. 161 (1973). See the reference(s) cited for biological (and synthetic) details.

"Rating" of Table 5, a symbol after one preceding it shows the activity when that preceding dose was halved. A capability for halving of doses several times without loss of activity of course is highly desirable, since any adverse side effects might disappear. The details of testing were summarized by Dr. Sweeney.[161]

The trail of research that led to the active classes in Table 5 began with the view of Eldjarn and Pihl that a key aspect of protection probably lies in the capability of radioprotective drugs to form disulfide linkages between the drugs and thiol groups of crucial but unknown biomolecules (refs. 160, 161). The fact that thiosulfonates readily thioalkylate thiols to give disulfides led us to Entry 1 of Table 5 (cf. eq. 10 and Secs. 5.1 and 13.4.2). Entry 1 was attractive enough that a large-scale preparation was developed.[130] Entry 2, a logical extension, turned out to be less active; for example, Entry 1 showed + at 1/2 dose and was active orally (signified by an asterisk), but although Entry 2 showed + at 750 mg/kg it was inactive at half that dose. The finding of promise by WRAIR for *n*-decylaminoethyl groups in other series led us to the further extension of Entry 3. In contrast to the activities of Entries 1–3, Table 6 shows that several related thiosulfonates were unpromising. This specificity of structure required for activity carries over to many other series, as one can see by comparing Tables 5 and 6 (cf. also, ref. 161, p. 671–672); such specificity implies mechanisms of action considerably more profound than simple nonspecific ones such as those of a mere antioxidant or a free-radical trap.

We concluded that the RSO_2 function of thiosulfonates acted as a "cover function" for the SR function. Eq. 57, a reminder of the well known exchange reaction of thiols with disulfides,[29] shows that unsymmetrical disulfides, R^1SSR^2, resemble thiosulfonates as thioalkylating agents, so that one-half the disulfide can be regarded as a "cover function" for the other half. This parallel led us to synthesize the unsymmetrical disulfides of Entries 4–7.

$$R^1SH + R^2SSR^2 \rightleftharpoons R^1SSR^2 + R^2SH \qquad (57)$$

Entry 4 again made use of the *n*-decylaminoethyl group. Structural specificity is strikingly illustrated here by inactivity with a change of $(CH_2)_2$ for the $(CH_2)_3$,[38] as well as with related disulfides in Table 6.

In Entry 5, the cover group for an aminothiol was *o*-carboxyphenylthio, a group mentioned earlier in other connections (eq. 3; Secs. 2.2 and 5.1). There seemed a possibility that $—CO_2^-$ might be responsible for the promising activity of Entry 5 through neighboring group displacement of the 2-aminothiolate moiety, and inactivity of the ester seemed consistent;[15] however, the promising activity of the sulfonic acid counterpart (Entry 6) argues otherwise, since the low nucleophilicity of $—SO_3^-$ should preclude a neighboring group effect. Selectivity again is evidenced by the inactivity of other congeners of Entry 5: where the ring was cyclohexyl rather than aryl (ref. 161, p. 254),[168] where the amine was acetylated (ref. 161, p. 331), or where other ortho substituents were used (ref. 161: pp. 183, 184, 242, 245, 290);[16] inactivity also resulted when other thiols were

used instead of 2-aminoethanethiol to make congeners of Entry 5, e.g. 2-*n*-decylaminoethanethiol (ref. 161, p. 603), cysteine (ref. 161, p. 276), penicillamine (ref. 161, p. 378), *N*-acetylpenicillamine (ref. 161, p. 477), or α-pyridylmethanethiol (ref. 161, p. 433).

Structural specificity is further illustrated by the lack of promise of other disulfides related to Entries 4–7 shown in Table 6, particularly as to congeners of the trithiopercarbamate of Entry 7; promise resulted for Entry 7 with $R^1 = R^2 =$ H or Me, but not for numerous trithiopercarbamates (thiocarbamyl disulfides) with other groups.[23,79] Some other representative unpromising trithiopercarbamates are shown in Table 6; the first was a particular surprise because both components were active in other contexts (Table 5, Entries 7 and 12).

Use of aldehydes or ketones that form stable hydrates as cover groups for radioprotective thiols was mentioned in Sec. 2.2. A trifluoroacetaldehyde adduct was promising (Entry 8), but the analogous trichloro compound was less so (ref. 161, p. 37; ± at 200 mg/kg, but 0 at 100 mg/kg); several adducts from other carbonyl compounds that gave stable hydrates were inactive (ref. 161: pp. 57, 327, 545).[13] The activity of the dithioketal of Entry 9 (**15**) was unexpected because, as Sec. 4 indicated, one would suppose it to be too tightly locked to engender an active species. Entries 8 and 9 differed in concept from the thioalkylation concept of Entries 1–7, in that they were intended to be prodrugs as defined in Sec. 2.2.

Sulfenamides were explored as thioalkylating agents (Sec. 7.3), where R^1R^2N served as a cover group for an aminothiol function. Only Entry 10 was promising, although many sulfenamides of the structure $R^1R^2NS(CH_2)_2NHAc$ were tried (e.g. ref. 161: pp. 207, 219, 332, 374).[79]

The final cover group tried, 4-sulfinobutyl, proved extremely attractive, so much so that the first example, Entry 11 (**141**) was patented.[167] As Table 5 shows, Entry 11 was active orally, and the ip dose could be halved four times before activity was lost. The congener without the acetyl group was less promising (at 300 mg/kg +, then ±; ref. 161, p. 125).[54] Synthesis of such compounds was illustrated in eq. 19 and discussed in Sec. 5.3.1. Entries 12–25 of Table 5 show promising extensions that resulted from our sporadic research subsequently with sulfinate di- and trisulfides and related species.

Among Entries 12–25, Entry 12 showed that the 4-mercaptobutanesulfinate component of Entry 11 has considerable activity in its own right. Acetylcystamine, $AcNH(CH_2)_2SH$, the other component of Entry 11, has some also (ref. 161, p. 42; at 300 mg/kg, ±, then 0). However, with Entry 11, the total of 1 + 1 is not 2 but 3 or more, since it is considerably more promising than either component.

Entry 13 was synthesized with L-proline as a framework to learn whether stereoisomerism was likely to be important;[55] the forms in which $SS(CH_2)_4S(O)OMe$ was *cis* and *trans* to CO_2Me did not seem to differ enough to warrant future attention to stereoisomerism. Entry 14 showed that use of a benzene ring as equivalent to two of the four atoms of the butanesulfinate chain still gave a very promising compound. Entry 15, taken with Entries 7 and 12,

confirmed that the $AcNH(CH_2)_2$ group was expendable; R of Entry 15 could be *p*-$MeOC_6H_4$ (at 150 mg/kg, +, +, ±),[163] as well as the *p*-MeC_6H_4 shown, but not *p*-$MeOC_6H_4CH_2$, *p*-ClC_6H_4, 1-adamantyl, or *n*-decyl (Table 6).[162,163] Table 6 also shows essentiality of the SO_2Na group among the disulfide-sulfinic acids, through lack of promise of a sulfonic acid and sulfone derivative. Substitution of the butane chain in this class, at least with acetate, also gave poor results (Table 6).

Unexpectedly rapid disproportionation of **141** (Entry 11) is attributable to the neighboring group effect of SO_2Na discussed in Sec. 5.2.1 (cf. eq. 15). This facile reaction seemed likely to play an important role in protective activity, and we naturally became curious about the activities of the two symmetrical disulfides produced (eq. 58).

$$\underset{\textbf{141 (Entry 11)}}{AcNH(CH_2)_2SS(CH_2)_4SO_2Na} \rightleftharpoons \underset{\textbf{142}}{[AcNH(CH_2)_2S]_2} \quad (58)$$

$$+\ NaO_2S(CH_2)_nS_m(CH_2)_nSO_2Na$$

51 (for Entry 16, n=4 and m=2)

The disulfide **142** was inactive.[50] The other disulfide, Entry 16 (i.e. **51**, with $n = 4$ and $m = 2$), was somewhat promising.

The prospect of an easier synthesis of the trisulfide of Entry 17 (i.e. **51**, $n = 4$, $m = 3$) than of the disulfide of Entry 16 led to Entry 17 as the most interesting drug studied to this point. Of Entry 17, Sweeney wrote that it proved to be ". . . a highly active antiradiation compound that was atypical in that the molecule contained no nitrogen. The theoretical significance and potential utility of this finding have yet to be explored." (ref. 161, p. 5), and that it ". . . was outstanding, both when administered intraperitoneally or orally. Compounds that contain a thiol group or thiol derivative that can be bioactivated but contain no amino function would seem to have great theoretical importance with respect to mode of action. Since this area has been little investigated it would be worthy of further investigation." (ref. 161, pp. 688–689). The synthesis of Entry 17 was discussed in Sec. 6 and illustrated by eq. 23 ($n = 4$, $x = 1$, $m = 3$). The methyl ester also was active but less so, and the ethyl ester was still less promising.[162] Table 6 shows some representative unpromising trisulfide-sulfinate congeners.

In the Miscellaneous category of Table 6, not surprisingly compounds that contained only a trisulfide moiety[162] or sulfinate moiety[162,163] were unpromising, as were sulfinylalkyl (or thioalkyl) disulfides;[162,163] also unpromising were the intended prodrug amide and diacid shown (cf. Sec. 8),[14] as were the Bunte-type salts shown that were intended to be thioalkylating agents.

Entry 18, a trisulfide-sulfinate counterpart of the disulfide-sulfinate (Entry 14) had activity comparable to that of Entry 14. The promise of trisulfides such as

Entries 17 and 18 naturally led us to try still longer sulfur chains. The pentasulfide (Entry 19) was less promising than the trisulfide of Entry 17. Furthermore, for a drug, the rearrangement possible with structures like Entry 19 was a concern (as eq. 25 and Sec. 6 brought out, a trisulfide sulfinate can rearrange to a disulfide thiosulfonate, so that with *m* of eq. 23 = 4-5 some thiosulfonate probably was an impurity).

What, we wondered, would be the effect of enhancing coplanarity of —SO_2Na and —SS—, so that the neighboring group effect might be augmented? Entry 20 proved to be active, and the trisulfide counterpart was spectacularly so (Entry 21, X = H). Indeed, Entry 21 (X = H) was one of 42 compounds among the 4400 tested by WRAIR that produced at least 50% survival at one-fourth of the highest dose (ref. 161, p. 770; two others were Entries 11 and 17); unfortunately, high doses of Entry 21 produced undesirable side effects.[53] Where X of Entry 21 was Cl, the product was less active (ref. 161, pp. 624, 769; see also ref. 53).

After the closing date of the Sweeney compendium in 1973,[161] we studied numerous disulfides where one group was the 4-butanesulfinate and the other contained various functional groups. Entries 22–25 were the most promising of these (these activities in Table 5 are recast from those we reported to match others in Table 5).[162,163] For Entry 22, only a simple alkyl group was used. The *n*-butyl group shown evidently was atypical, because the *t*-butyl isomer was virtually inactive.[163] Entry 23, a bisdisulfide bissulfinate, is a sort of doubled-up version of Entry 16 (with *n* = 2, the activity of 150 mg/kg was ±, ±, +).[163] Entry 24, with a carboxyalkyl group, was somewhat promising; congeners with *n* = 3 and 5 also were made,[52] but the WRAIR program closed before they could be tested (a number of other compounds also unfortunately never could be tested: cf. refs. 36, 41, 51, 52, 66, 92, 100 and 103). Of considerable promise was the dihydroxypropyl compound (Entry 25). Entries 23, 24, and 25 were considered sufficiently promising to be patented (respectively, refs. 164, 165, and 166). Our final active drug was Entry 26; it resembles Entry 23, but since —S(O)— takes the place of —SO_2Na the —S(O)— group presumably shares at least to some extent the neighboring-group effect attributed to —SO_2Na. Interestingly, a monosulfinyl disulfide was inactive (Table 6, Miscellaneous).

A very intriguing feature of compounds developed as "antirads" is the variety of other significant biological activities several displayed: suppression of enzymes, of microorganisms, and of immune systems,[162] as well as (unpublished) anti-HIV and anticancer activity (the latter for Entry 11 of Table 5; Nat'l Cancer Center of the N.I.H., No. 342,029). This breadth implies basic biochemical involvement(s) that are as yet unknown and seems to deserve both biological probing and further study for medicinal applications.

16.4. *Other Biological Aspects*

Mutagenicity by thioamides was discussed in Sec. 3 and by thionophosphorus compounds in Sec. 9.3.

17. MISCELLANEOUS

As the German word "Kraft" for strength implies, kraft paper is the tough brown type used for heavy-duty sacks, wrapping paper, and the like. It is made from wood pulp by "cooking" with alkaline sodium sulfide to remove lignin, which acts as a cement in wood for the cellulose fibers and amounts to about 24–35% of the mass of softwoods. Key points of the kraft process are that sodium sulfide accelerates delignification but not attack on carbohydrate, and that sulfur enters the lignin molecule (cf. ref. 169). Removal of the "black liquor" formed in the cooking process leaves the cellulose, which is spread and dried to give kraft paper. Acidification of the liquor precipitates "thiolignin." What sodium sulfide does in removing lignin as thiolignin is not only of chemical interest but of commercial importance, since after cellulose lignin is the most abundant organic material on earth, and vast amounts of thiolignin are simply left in the "black liquor" only to be burned as fuel as the inorganic chemicals are recovered. Piqued by curiosity as to the nature of thiolignin, and challenged as well by implications for the structure of lignin itself and for eventual uses of thiolignin, we begged 400 pounds of commercial pine thiolignin; it was reported to be of relatively uniform properties. We first looked at its composition,[169] since little was known about the simplicity or complexity of thiolignin. Fractionation by solvents was promising, but not for large amounts such as the 2500 g we finally used. Instead,[169] we first obtained three fractions by acidifying an alkaline solution. One of these we then fractionally extracted into acetone, and, finally, we chromatographed an acetone-soluble fraction with several solvents to give nine fractions. Ranges from the beginning of all of the separations were 700–1200 in molecular weight, 186–237 in equivalent weight (as acidic functions), and 0.76–1.35 in percent sulfur. We concluded that the thiolignin was a complex mixture of a considerable number of similar substances, which nevertheless were distinguishably different in the properties already mentioned, as well as in infrared spectra and decomposition point (range, 110 °C to above 235 °C).

For structural studies,[170] since no one of the fractions was more attractive than another, and also so that all of the initial sulfur functions still would be present, we reverted to the initial commercial thiolignin. At least four different kinds of sulfur function appeared to be present; thus hot water removed about a tenth of the sulfur, dilute alkali removed about one-fourth, Raney nickel in dioxane about half, and Raney nickel in dilute alkali about three-fourths; the remaining fourth seemed to be particularly stable.[170] Comparison of infrared spectra of methylated thiolignin before and after oxidation indicated presence of sulfoxide and perhaps sulfone linkages initially.[170] Only negligible elementary sulfur or sulfide ion was present, and various reactions appeared to rule out significant amounts of thiol, disulfide, polysulfide, thiocarbonyl, or dialkyl sulfide.[170] Pyrolysis gave three products, each in ca. 2% yield, which were fairly homogeneous and seem to deserve a further look.[170]

Sulfur species that might be added in this final section, mentioned earlier only *en passant*, are **sulfonium salts**, **sulfur ylides** and **singlet (atomic) sulfur**, **S(^{1}D)**.

Sec. 15.2 referred to conversion of a sulfide to a **sulfonium salt** without interference from a disulfide linkage in the molecule and to lack of transannular interaction between the two thereafter. Sec. 5.2.2. referred to insertion and other reactions of disulfides with **sulfur ylides**, which were synthesized from various sulfonium salts (and in other ways).[57]

Sec. 9.1 alluded to photolysis of carbonyl sulfide to give **singlet sulfur**, $S(^1D)$ (eq. 59), along with our conclusion that formation and reactions of $S(^1D)$ did

$$COS \xrightarrow{h\nu} S(^1D) + CO \tag{59}$$

not explain the biological damage that can ensue from biooxidation of thiono phosphorus compounds. Elegant studies by Gollnick, Leppin, and Schomburg had shown eq. 59 to be a good source of $S(^1D)$, which could be trapped by insertion into cyclohexane to give cyclohexanethiol. Since our initial thought had been that $S(^1D)$ might explain the biological damage mentioned, we sought optimum traps for it, feeling that lack of effect by a good trap on suspected reactions would argue against participation of $S(^1D)$, while blocking of such reactions by a trap would argue for participation.[84] Relative effectiveness of a candidate as a trap was assessed by competition with cyclohexane for insertion of sulfur when both were used concurrently as solvent with eq. 59. The order of decreasing promise as traps for $S(^1D)$ proved to be the following: n-Bu_3SnH > $(n\text{-}C_5H_{11}S)_2$ ≈ RSH > $(EtO)_3SiH$ > Et_3SiH ≈ cyclohexane;[84] later,[85] an alkene moiety also was tried as a trap for atomic sulfur (again with a lack of success that confirmed absence of atomic sulfur after oxidation of a thiono phosphorus compound). Although $S(^1D)$ did indeed convert thiols to hydrodisulfides (RSSH),[84] as Neal had postulated for biological damage caused by atomic sulfur from thiono phosphorus compounds,[171] we concluded that other reactions were more likely to be responsible for the damage (cf. Sec. 9.2; damage by other mechanisms were discussed for the classes of thioamides in Sec. 3 and of thiono imidazole derivatives in Sec. 9.1).

Other encounters with organosulfur chemistry have included service on editorial boards of *Sulfur Letters*, *Sulfur Reports*, and *Phosphorus, Sulfur, Silicon and the Related Elements*, along with reviews that I hope still will afford useful references on disulfides,[29] on the sulfur-iodine bond,[75] and on syntheses involving major classes of organosulfur compounds.[114,115]

18. ACKNOWLEDGMENTS

It is both a duty and pleasure to acknowledge the clearly essential contributions of originality, chemical expertise, and hard work made by the talented and congenial undergraduates, graduate students, postdoctoral associates, and colleagues to the papers cited that bear their names. Thanks are due to Prof. D. S. Tarbell who commented helpfully on this MS. and to Mrs. Connie Beasley who typed

it, as well as to all of the staff of the Department of Chemistry for effective support over the years.

Gratitude must be stressed for the faith in our research group that led to generous financial support at various times from the following (in alphabetical order): The Carnegie Foundation; Merck and Co., Inc.; the National Institutes of Health through several institutes; the National Science Foundation; Research Corporation (our first grantor, ca. 1950); the Technical Association of the Pulp and Paper Industry; the U.S. Army, through the Office of Ordnance Research (later, the Army Research Office), and through the Medical Research and Development Command (over some 22 years; with special appreciation to D. P. Jacobus, R. O. Pick, T. R. Sweeney, E. A. Steck, and M. Musallam); Vanderbilt University is due thanks through the Center in Molecular Toxicology and the Research Council. Apart from these, fellowships named in the references cited meant a great deal in our work.

Thanks are due to my parents, who encouraged my early home-laboratory efforts despite an occasional fire and explosion, and to my scientific mentors (T. R. P. Gibb, Jr., J. C. Sheehan, and A. C. Cope, among others) who showed similar forbearance and provided inspiration and guidance. And finally, deep gratitude is due to my wife Betty, my daughter Patricia, and my son Brock for their understanding and patience during the long hours away from one's family that serious research efforts require; Betty also was of great help with the indexes.

19. REFERENCES

1. J. C. Sheehan, *The Enchanted Ring. The Untold Story of Penicillin* (The MIT Press, Cambridge, Mass., 1982).
2. A. H. Cook in *The Chemistry of Penicillin*, H. T. Clarke, J. R. Johnson, and R. Robinson, Eds. (Princeton University Press, Princeton, N.J., 1949), pp. 123, 142. Wartime research reports of the group at Merck and Co. to the Office of Scientific Research and Development to which L. Field is listed as a contributor are indexed on p. 1058.
3. R. Connor in *Organic Chemistry. An Advanced Treatise*, H. Gilman, Ed. (John Wiley and Sons, New York, 1943), 2nd ed., Vol. I, Chapt. 10.
4. A. C. Cope, D. E. Morrison, and L. Field, *J. Am. Chem. Soc.*, **72**, 59 (1950).
5. J. R. Cox, Jr., C. L. Gladys, L. Field, and D. E. Pearson, *J. Org. Chem.*, **25**, 1083 (1960).
6. J. R. Cox, Jr., C. L. Gladys, L. Field, and D. E. Pearson, *J. Org. Chem.*, **25**, 2263 (1960).
7. L. Field and P. R. Engelhardt, *J. Org. Chem.*, **35**, 3647 (1970).
8. L. Field and C. B. Hoelzel, *J. Org. Chem.*, **23**, 1575 (1958).
9. G. A. Dilbeck, L. Field, A. A. Gallo, and R. J. Gargiulo, *J. Org. Chem.*, **43**, 4593 (1978).
10. W. E. Truce and F. M. Perry, *J. Org. Chem.*, **30**, 1316 (1965).
11. V. Stella in *Prodrugs as Novel Drug Delivery Systems*, T. Higuchi and V. Stella, Eds. (American Chemical Society, Washington, D.C., 1975), p. 92.
12. L. Field and B. J. Sweetman, *J. Org. Chem.*, **34**, 1799 (1969).
13. L. Field, B. J. Sweetman, and M. Bellas, *J. Med. Chem.*, **12**, 624 (1969).
14. P. K. Srivastava and L. Field, *J. Med. Chem.*, **16**, 428 (1973).
15. R. R. Crenshaw and L. Field, *J. Org. Chem.*, **30**, 175 (1965).
16. L. Field and H. K. Kim, *J. Med. Chem.*, **9**, 397 (1966).
17. L. Field and P. M. Giles, Jr., *J. Org. Chem.*, **36**, 309 (1971).
18. L. Field and R. O. Beauchamp, Jr., *J. Am. Chem. Soc.*, **74**, 4707 (1952).
19. L. Field in *Encyclopedia of Chemical Technology*, R. E. Kirk and D. F. Othmer, Eds. (The Interscience Encyclopedia, Inc., New York, N.Y., 1955), **14**, pp. 58–67.

20. P. Noble, Jr., and D. S. Tarbell, *Org. Synth.*, **32**, 101 (1952).
21. L. Field, W. S. Hanley, I. McVeigh, and Z. Evans, *J. Med. Chem.*, **14**, 202 (1971).
22. L. Field and J. D. Buckman, *J. Org. Chem.*, **32**, 3467 (1967).
23. L. Field and J. D. Buckman, *J. Org. Chem.*, **33**, 3865 (1968).
24. L. Field, W. S. Hanley, and I. McVeigh, *J. Med. Chem.*, **14**, 995 (1971).
25. L. Field, W. S. Hanley, and I. McVeigh, *J. Org. Chem.*, **36**, 2735 (1971); the use of AcSCl was based on the work of H. Böhme and M. Clement, *Justus Liebigs Ann Chem.*, **576**, 61 (1952).
26a. J. H. Hillhouse, I. A. Blair, and L. Field, *Phosphorus Sulfur*, **26**, 169 (1986).
26b. M. C. Dyroff and R. A. Neal, *Mol. Pharmacol.*, **23**, 219 (1983).
27. A. P. Breau, W. M. Mitchell, D. W. Karkhanis, and L. Field, *Mut. Res. (Lett.)*, **139**, 1 (1984).
28. B. J. Sweetman, M. Bellas, and L. Field, *J. Med. Chem.*, **12**, 888 (1969).
29. L. Field in *Organic Chemistry of Sulfur*, S. Oae, Ed. (Plenum Press, New York, 1977), Chapt. 7.
30. T. F. Parsons, J. D. Buckman, D. E. Pearson, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965).
31. L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).
32. L. Field, H. Härle, T. C. Owen, and A. Ferretti, *J. Org. Chem.*, **29**, 1632 (1964).
33. Y. H. Khim and L. Field, *J. Org. Chem.*, **37**, 2714 (1972).
34. L. Field, T. F. Parsons, and D. E. Pearson, *J. Org. Chem.*, **31**, 3550 (1966).
35. L. Field, A. Ferretti, and T. C. Owen, *J. Org. Chem.*, **29**, 2378 (1964).
36. P. K. Singh and L. Field, *J. Chem. Eng. Data*, **32**, 67 (1988).
37. P. K. Srivastava and L. Field, *J. Chem. Eng. Data*, **31**, 252 (1986).
38. L. Field, H. K. Kim, and M. Bellas, *J. Med. Chem.*, **10**, 1166 (1967).
39. P. K. Singh, L. Field, and B. J. Sweetman, *J. Org. Chem.*, **53**, 2608 (1988).
40. P. K. Singh, T. Q. Nguyen, L. Field, and B. J. Sweetman, *Sulfur Lett.*, **8**, 107 (1988).
41. P. K. Singh, L. Field, and B. J. Sweetman, *Phosphorus Sulfur*, **39**, 61 (1988).
42. L. Field, J. A. R. Grimaldi, Jr., W. S. Hanley, M. W. Holladay, R. Ravichandran, L. J. Schaad, and C. E. Tate, *J. Med. Chem.*, **20**, 996 (1977).
43. L. Field and J. E. Lawson, *J. Am. Chem. Soc.*, **80**, 838 (1958).
44. L. Field and R. Ravichandran, *J. Org. Chem.*, **44**, 2624 (1979).
45. P. K. Srivastava and L. Field, *J. Org. Chem.*, **37**, 4196 (1972).
46. T. W. G. Solomons, *Organic Chemistry* (John Wiley and Sons, New York, 1980), 2nd ed., p. 147.
47. M. Bellas, D. L. Tuleen, and L. Field, *J. Org. Chem.*, **32**, 2591 (1967).
48. L. Field, P. M. Giles, Jr., and D. L. Tuleen, *J. Org. Chem.*, **36**, 623 (1971).
49. J. D. Macke and L. Field, *Phosphorus Sulfur*, **37**, 27 (1988).
50. L. Field and Y. H. Khim, *J. Med. Chem.*, **15**, 312 (1972).
51. R. Chandra and L. Field, *Phosphorus Sulfur*, **27**, 247 (1986).
52. J. D. Macke and L. Field, *J. Org. Chem.*, **53**, 396 (1988).
53. P. K. Srivastava, L. Field, and M. M. Grenan, *J. Med. Chem.*, **18**, 798 (1975).
54. L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 1792 (1969).
55. V. Eswarakrishnan and L. Field, *J. Org. Chem.*, **46**, 4182 (1981).
56. L. Field and C. H. Banks, *J. Org. Chem.*, **40**, 2774 (1975).
57. L. Field and H.-K. Chu, *J. Org. Chem.*, **42**, 1768 (1977).
58. L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 36 (1969).
59. L. Field and Y. H. Khim, *J. Org. Chem.*, **37**, 2710 (1972).
60. N. E. Heimer, L. Field, and R. A. Neal, *J. Org. Chem.*, **46**, 1374 (1981).
61. Cf. W. A. Pryor, *Mechanisms of Sulfur Reactions* (McGraw Hill, New York, 1962), pp. 62–63.
62. N. E. Heimer and L. Field, *J. Org. Chem.*, **49**, 1446 (1984).
63. N. E. Heimer, L. Field, and J. A. Waites, *J. Org. Chem.*, **50**, 4164 (1985).
64. L. Field and H. K. Kim, *J. Org. Chem.*, **31**, 597 (1966).
65. L. Field and G. T. Bowman, *J. Org. Chem.*, **46**, 2771 (1981).
66. R. Chandra and L. Field, *J. Org. Chem.*, **51**, 1844 (1986).
67. L. Field and T. F. Parsons, *J. Org. Chem.*, **30**, 657 (1965).
68. D. E. Pearson, D. Caine, and L. Field, *J. Org. Chem.*, **25**, 867 (1960).
69. L. Field, *J. Org. Chem.*, **39**, 2110 (1974).
70. J. D. Buckman and L. Field, *J. Org. Chem.*, **32**, 454 (1967).
71. G. T. Bowman and L. Field, *J. Org. Chem.*, **47**, 222 (1982).
72. L. Field and V. Eswarakrishnan, *J. Org. Chem.*, **46**, 2025 (1981).
73. L. Field and V. Eswarakrishnan, *J. Org. Chem.*, **53**, 5192 (1988).

74. L. Field, J. L. VanHorne, and L. W. Cunningham, *J. Org. Chem.*, **35**, 3267 (1970).
75. L. Field and C. M. Lukehart in *Sulfur in Organic and Inorganic Chemistry*, A. Senning, Ed. (Marcel Dekker, Inc., New York, 1982), Vol. 4, pp. 340–353.
76. L. Field and J. E. White, *Proc. Nat. Acad. Sci. USA*, **70**, 328 (1973).
77. L. Field and J. E. White, *Int. J. Sulfur Chem.*, **8**, 539 (1976).
78. L. Field, R. V. Dilts, R. Ravichandran, P. G. Lenhert, and G. E. Carnahan, *J. Chem. Soc., Chem. Commun.*, 249 (1978).
79. N. E. Heimer and L. Field, *J. Org. Chem.*, **35**, 3012 (1970).
80. W. D. Stephens and L. Field, *J. Org. Chem.*, **24**, 1576 (1959).
81. L. Field and A. A. Gallo, *J. Fluorine Chem.*, **15**, 29 (1980).
82. L. H. Brannigan, R. B. Hodge, and L. Field, *J. Med. Chem.*, **19**, 798 (1976).
83. D. W. Karkhanis and L. Field, *Phosphorus Sulfur*, **22**, 49 (1985).
84. L. Field, J. V. Ravan, J. D. Dunkel, J. A. Waites, D. W. White, N. E. Heimer, and R. A. Neal, *J. Org. Chem.*, **47**, 4651 (1982).
85. L. Field, N. E. Heimer, R. I. McNeil, R. A. Neal, J. Swinson, and J. R. Van Wazer, *Sulfur Lett.*, **1**, 135 (1983).
86. J. Swinson, L. Field, N. E. Heimer, D. Michalska, D. D. Muchio, P. L. Polavarapu, M. P. Stone, and J. R. Van Wazer, *Phosphorus Sulfur*, **35**, 159 (1988).
87. J. Swinson, L. Field, N. E. Heimer, M. P. Stone, and J. R. Van Wazer, *Phosphorus, Sulfur Silicon Relat. Elem.*, **44**, 39 (1989).
88. A. P. Breau, L. Field, and W. M. Mitchell, *Cell. Biol. Toxicol.*, **1**, 13 (1984).
89. A. P. Breau, W. M. Mitchell, J. Swinson, and L. Field, *J. Toxicol. Environ. Health*, **16**, 403 (1985).
90. W. M. Mitchell, A. P. Breau, J. Swinson, and L. Field, *Phosphorus Sulfur*, **35**, 151 (1988).
91. R. Chandra and L. Field, *Sulfur Lett.*, **3**, 169 (1985).
92. L. Field and C. Lee, *J. Org. Chem.*, **55**, 2558 (1990).
93. C. Lee, D. B. Stidham, and L. Field, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **47**, 53 (1990).
94. C. Lee and L. Field, *Synthesis*, 391 (1990); editorial errata, 1204.
95. L. Field and P. H. Settlage, *J. Am. Chem. Soc.*, **73**, 5870 (1951).
96. L. Field, C. B. Hoelzel, J. M. Locke, and J. E. Lawson, *J. Am. Chem. Soc.*, **83**, 1256 (1961).
97. L. Field, C. B. Hoelzel, and J. M. Locke, *J. Am. Chem. Soc.*, **84**, 847 (1962).
98. L. Field and J. M. Locke, *Org. Synth.*, **46**, 62 (1966).
99. L. Field, J. M. Locke, C. B. Hoelzel, and J. E. Lawson, *J. Org. Chem.*, **27**, 3313 (1962).
100. J. P. Harmon and L. Field, *J. Org. Chem.*, **51**, 5235 (1986).
101. P. K. Srivastava and L. Field, *Phosphorus Sulfur*, **25**, 161 (1985).
102. P. G. Lenhert, A. E. Morales, J. P. Harmon, and L. Field, *Acta Cryst. C* **42**, 1637 (1986).
103. C. Lee and L. Field, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **45**, 35 (1989).
104. J. M. Hoch and L. Field, *J. Org. Chem.*, **48**, 2601 (1983).
105. L. Field, *J. Am. Chem. Soc.*, **74**, 3919 (1952).
106. L. Field and J. W. McFarland, *J. Am. Chem. Soc.*, **75**, 5582 (1953).
107. L. Field, *J. Am. Chem. Soc.*, **78**, 92 (1956).
108. L. Field, J. E. Lawson, and J. W. McFarland, *J. Am. Chem. Soc.*, **78**, 4389 (1956).
109. L. Field, J. R. Holsten, and R. D. Clark, *J. Am. Chem. Soc.*, **81**, 2572 (1959).
110. L. Field and E. T. Boyd, *J. Org. Chem.*, **26**, 1787 (1961).
111. L. Field and E. T. Boyd, *J. Org. Chem.*, **29**, 3273 (1964).
112. L. Field and R. D. Clark, *J. Org. Chem.*, **22**, 1129 (1957).
113. L. Field and R. D. Clark, *Org. Synth.*, **38**, 62 (1958).
114. L. Field, *Synthesis*, 101 (1972).
115. L. Field, *Synthesis*, 713 (1978).
116. D. H. McGlory, N. S. Olsen, and L. Field, *J. Tenn. Acad. Sci.*, **28**, 208 (1953).
117. L. Field and J. P. Harmon, *Sulfur Lett.*, **1**, 181 (1983).
118. L. Field, T. F. Parsons, and R. R. Crenshaw, *J. Org. Chem.*, **29**, 918 (1961).
119. L. Field, *J. Am. Chem. Soc.*, **74**, 394 (1952).
120. L. Field and J. W. McFarland, *Org. Synth.*, **36**, 91 (1956).
121. L. Field and P. H. Settlage, *J. Am. Chem. Soc.*, **76**, 1222 (1954).
122. L. Field and P. H. Settlage, *J. Am. Chem. Soc.*, **77**, 170 (1955).
123. L. Field and F. A. Grunwald, *J. Org. Chem.*, **16**, 946 (1951).
124. L. Field and J. R. Holsten, *J. Am. Chem. Soc.*, **77**, 1286 (1955).
125. D. E. Pearson, W. G. DePierri, Jr., and L. Field, *J. Tenn. Acad. Sci.*, **30**, 234 (1955).
126. L. Field and F. A. Grunwald, *J. Am. Chem. Soc.*, **75**, 934 (1953).

127. L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).
128. W. G. Christiansen and M. A. Dolliver, U.S. Patent 2,242,236 (1941); *Chem. Abst.*, **35**, 5647 (1941).
129. R. R. Crenshaw and T. C. Owen, *Proc. Chem. Soc. London*, 250 (1961).
130. L. Field, T. C. Owen, H. Härle, and R. R. Crenshaw, *Biochem. Prep.*, **11**, 7 (1966).
131. I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **24**, 973 (1959).
132. J. D. Buckman, M. Bellas, H. K. Kim, and L. Field, *J. Org. Chem.*, **32**, 1626 (1967).
133. L. Field and W. B. Lacefield, *J. Org. Chem.*, **31**, 599 (1966).
134. L. Field and W. B. Lacefield, *J. Org. Chem.*, **31**, 3555 (1966).
135. J. A. Durden, Jr., H. A. Stansbury, Jr., and W. H. Catlette, *J. Am. Chem. Soc.*, **81**, 1943 (1959).
136. T. C. Owen, C. L. Gladys, and L. Field, *J. Chem. Soc.*, 501 (1962).
137. L. Field, *Sulfur Rep.*, **11**, 355 (1992); some references are included to later reports of α,β-epithio esters.
138. In related work, others felt that unsaturated products of structure **121** came from intermediates other than the desired α,β-epithio ester: C. C. Tung and A. J. Speziale, *J. Org. Chem.*, **29**, 1577 (1964).
139. T. C. Owen, C. L. Gladys, and L. Field, *J. Chem. Soc.*, 656 (1962).
140. L. Field, W. S. Hanley, P. L. Kelly, W. J. Sanders, J. E. White, I. A. Jaffe, and P. Merryman, *J. Med. Chem.*, **16**, 1152 (1973).
141. N. E. Heimer and L. Field, *J. Org. Chem.*, **35**, 1668 (1970).
142. L. Field and C. H. Foster, *J. Org. Chem.*, **35**, 749 (1970).
143. L. Field and D. L. Tuleen in *Seven-membered Heterocylic Compounds Containing Oxygen and Sulfur*, edited by A. Rosowsky (John Wiley and Sons, New York, 1972), pp. 573–666.
144. L. Field, W. D. Stephens, and E. L. Lippert, Jr., *J. Org. Chem.*, **26**, 4782 (1961).
145. J. D. Buckman, B. S. Johnson, and L. Field, *Can. J. Microbiol.*, **12**, 1263 (1966).
146. For reviews and references, see the Ph.D. dissertations (Vanderbilt University) of W. S. Hanley (1971, pp. 7–12) and R. Ravichandran (1979, pp. 8–12).
147. I. McVeigh, L. Field, and W. S. Hanley in *Histoplasmosis. Proceedings of the Second National Conference*, edited by L. Ajello, E. W. Chick, and M. L. Furcolow (Charles C. Thomas, Springfield, Ill., 1971), Chapter 11.
148. I. McVeigh, Z. Evans, L. Field, and W. Hanley, *Mycopathol. Mycol. Appl.*, **37**, 349 (1969).
149. I. McVeigh, S. Evans, L. Field, W. S. Hanley, and C. E. Tate, *J. Med. Chem.*, **15**, 431 (1972).
150. L. J. Schaad, R. H. Werner, L. Dillon, L. Field, and C. E. Tate, *J. Med. Chem.*, **18**, 344 (1975).
151. B. J. Sweetman, M. M. Vestling, S. T. Ticaric, P. L. Kelly, L. Field, P. Merryman, and I. A. Jaffe, *J. Med. Chem.*, **14**, 868 (1971).
152. W. S. Hanley, P. L. Kelly, W. J. Sanders, J. E. White, and L. Field, *Int. J. Sulfur Chem.*, **A**, **2**, 213 (1972).
153. C. R. Cothern, W. E. Moddeman, R. G. Albridge, W. J. Sanders, P. L. Kelly, W. S. Hanley, and L. Field, *Anal. Chem.*, **48**, 162 (1976).
154. W. S. Hanley, M. E. Snyder, L. Field, and A. A. Gallo, *Chem.-Biol. Interact.*, **21**, 263 (1978).
155. M. W. Whitehouse, W. S. Hanley, and L. Field, *Arthritis Rheum.*, **20**, 1035 (1977).
156. M. W. Whitehouse, L. Field, C. W. Denko, and R. Ryall, *Scand. J. Rheumatol.*, Supplement 8, Abstracts of the VIIIth European Rheumatology Congress, Helsinki, No. 183 (1975).
157. R. E. Weiss, L. Field, A. Gorn, C. Williams, S. Dux, R. Ravichandran, A. A. Gallo, V. Eswarakrishnan, and M. E. Nimni, *Biochem. Med.*, **32**, 331 (1984).
158. D.-M. Chen, G. DiSabato, L. Field, A. A. Gallo, and S. Harshman, *Clin. exp. Immunol.*, **30**, 317 (1977).
159. L. Field, A. A. Gallo, F. W. J. Beck, and M. W. Whitehouse, *Chem.-Biol. Interac.*, **23**, 215 (1978).
160. D. L. Klayman and E. S. Copeland in *Kirk-Othmer Encyclopedia of Chemical Technology*, Vol. 19, 3rd ed., M. Grayson, Ed. (Wiley-Interscience, New York, 1982), pp. 801–832.
161. T. R. Sweeney, *A Survey of Compounds from the Antiradiation Drug Development Program of the U.S. Army Medical Research and Development Command* (Walter Reed Army Institute of Research, Washington, D.C., 1979).
162. G. T. Bowman, J. J. Clement, D. E. Davidson, Jr., V. Eswarakrishnan, L. Field, J. M. Hoch, H. A. Musallam, R. O. Pick, R. Ravichandran and P. K. Srivastava, *Chem.-Biol. Interact.*, **57**, 161 (1986).

163. R. Chandra, J. J. Clement, L. Field, J. P. Harman, H. A. Musallam, and P. K. Srivastava, *Sulfur Lett.*, **9**, 87 (1989).
164. L. Field, H. A. Musallam, J. D. Macke, and P. K. Srivastava, U.S. Patent 4,978,782 (1990); a division from ref. 165.
165. L. Field, H. A. Musallam, J. D. Macke, and P. K. Srivastava, U.S. Patent 4,883,890 (1989); *Chem. Abstr.*, **112**, 197625 (1990).
166. L. Field, H. A. Musallam, J. D. Macke, and P. K. Srivastava, U.S. Patent 4,943,657 (1990); a division from ref. 165.
167. L. Field and R. B. Barbee, U.S. Patent 3,723,513 (1973); *Chem. Abstr.*, **78**, 158919 (1973).
168. L. Field and P. M. Giles, Jr., *J. Med. Chem.*, **13**, 317 (1970).
169. L. Field, P. E. Drummond and P. H. Riggins, with E. A. Jones, *Tappi*, **41**, 721 (1958).
170. L. Field and P. E. Drummond, with E. A. Jones, *Tappi*, **41**, 727 (1958).
171. R. A. Neal in *The Scientific Basis of Toxicity Assessment*, edited by H. Witschi (Elsevier/North-Holland Biomedical Press, Amsterdam, 1980), Vol. 6, pp. 241–250.