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Sulfur, an Important Element in my Life

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SULFUR, AN IMPORTANT ELEMENT IN MY LIFE

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The present review constitutes the author's chemical autobiography with 239 references to his papers, patents, and books dating from 1960 to 2003.

Keywords: Acetylsalicylic acid; Anti-Pummerer reaction; Carbon monosulfide; Chlorodithioformates; Cyclopentadienethiones; Dithiiranes; Hexathiepanes; 1,3,4-Oxathiazol-2-ones; Pentathianes; Quasi-Wittig reaction; Sulfenic acid derivatives; Sulfines; Sulfinic acid derivatives; *N*-Sulfinyl compounds; Sulfonic acid derivatives; *C*-Sulfonyldithioformates; *C*-Sulfonylthioformamides; Sulfur diimides; Tetrathiolanes; Thiocarbamoyl chlorides; Thiocarbonyl *S*-disulfides; Thiocarbonyl *S*-imides; Thiocarbonyl *S*-ylides; Thioketenes; Thiopeptides; Thiophenes; Thiosulfines; *N*-Thiosulfinyl compounds; Trithietanes, Trithiocarbonic acid derivatives

CONTENTS

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1. INTRODUCTION

In my former capacity as the editor of this journal I occasionally approached senior colleagues with a request for a chemical autobiography and more often than not I received the reply that neither did they feel *that* old nor did they accept that the label *sulfur chemist* could be rightfully applied to them. Now that it seems to be my turn I feel the same concerning my age, but I certainly do not shun the label *sulfur chemist* even though I occasionally pursued non-sulfur interests in chemistry (*vide infra*).

After undergraduate studies at the University of Munich, Germany, in 1954–1959 I pursued postgraduate studies at the Department of Chemistry, Uppsala University, Sweden, where I obtained a fil.lic. (PhD) degree in organic chemistry in 1962. In the same year I joined the Department of Chemistry, Aarhus University, Denmark, as Assistant Professor where I was appointed Associate Professor in 1965. While on leave from Aarhus University in 1973–1975 I worked for the now defunct drug company A/S Alfred Benzon, Copenhagen, Denmark, as manager of their research and development laboratory devoted to drugs, cosmetics and confectionery. In 1993 I accepted a professorship in organic chemistry at the Engineering Academy of Denmark in Lyngby, Denmark, which later became integrated into the Technical University of Denmark, my current affiliation.

I was introduced to sulfur chemistry in 1960 as a graduate student in the laboratory of my supervisor Sven-Olov Lawesson in Uppsala where my first task was to prepare potentially fungicidal aryl trichloromethyl sulfides, $ArSCCl_3$, **1** in analogy to the known preparation of phenyl trichloromethyl sulfide, $PhSCCl_3$, **1a** from phenylmagnesium bromide and trichloromethanesulfenyl chloride, CCl_3SCl, **2**. It turned out that the key paper [1] which had triggered our research program was not just in error but apparently written in bad faith, an experience which taught me healthy skepticism towards capricious claims in printed sources [2]. The desired **1** could then be prepared undramatically by chlorination of aryl methyl sulfides, ArSMe, **3** under standard conditions [3–5]. We could furthermore show that authentic **1a** reacts with phenylmagnesium bromide to form diphenyl sulfide, not too surprising considering the pseudo- or superhalogen nature of a trichloromethyl group. The experience gained with **2**, a highly functionalized C_1 compound, however, led to a number of interesting projects in my later independent work.

A parallel interest in medicinal chemistry developed via work with cytostatic sulfonic acid alkylene esters [6–10] and extended later to potential aspirin prodrugs [11–17], nootropics [18–20], etc.

The journals *Sulfur Reports* and *Sulfur Letters* were founded by me (in cooperation with the publishers Gordon & Breach) in 1980 and 1982, respectively, and I edited both journals until 1999.

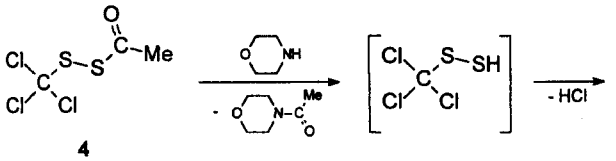
2. $R^1R^2CS_n$ SYSTEMS

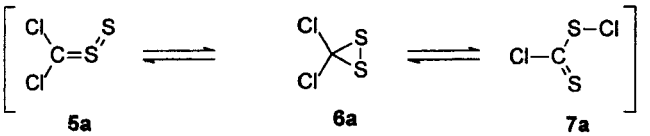
2.1. Dithiiranes–Thiosulfines

Since this subject has recently been extensively reviewed Sections 2.1.1 and 2.1.2 are not intended to duplicate this effort. For details see the relevant reviews [21–23]. Our thoughts about the interrelationship between dithiiranes, thiosulfines and dithiocarboxylates (or dithiocarboxylate analogs) have been seminal for the vigorous

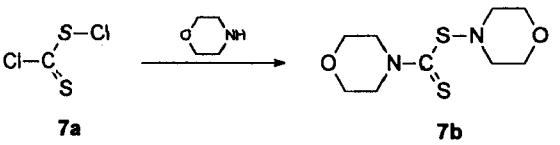
development of this area of sulfur chemistry over the years. Especially fruitful was our later cooperation with Jürgen Fabian (Technical University Dresden, Germany) and Grzegorz Mloston (University of Lodz, Poland).

2.1.1. Early Findings





(1)



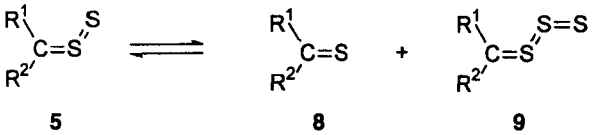
(2)

SCHEME 1

Our original concept of the thiosulfine **5**–dithiirane **6**–dithioester **7** manifold (Scheme 1) was first proposed in 1979 when we elucidated the 'unzipping' of acetyl trichloromethyl disulfide **4** with morpholine (equations (1) and (2)) [24]. In subsequent years this concept proved very fruitful indeed, both in our laboratory and elsewhere. On the other hand, our progress was somewhat hampered by the fact that the majority of our reactive S_2 intermediates lost sulfur to yield trivial S_1 compounds as the isolable final products. Another difficulty was our apparent inability to trap the same reactive S_2 intermediates in appropriate cycloaddition reactions [21,25].

2.1.2. Recent Results

The subject was revitalized by a number of exciting findings in other laboratories: Huisgen's discovery of the equilibrium

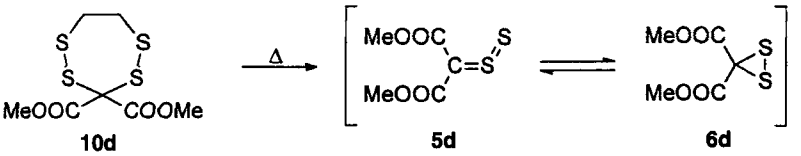


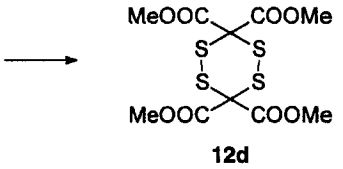
(3)

and the successful trapping of both thiosulfines **5** and thiocarbonyl *S*-disulfides **9** by cycloaddition to dipolarophiles [21–23], by Nakayama's and Ishii's preparation and isolation of sterically hindered dithiiranes **6** [21–23] and, most recently, by

Mloston *et al.*'s and Maier's direct observation of the thiosulfine **5c**–dithiirane **6c**–dithioformic acid **7c** manifold [26].

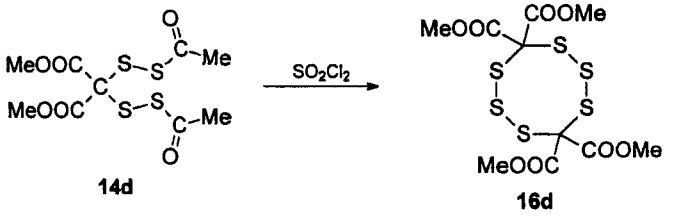
The pyrolysis of bis(dithio)-substituted malonic acid derivatives such as **10d** (obtained from *gem*-bis(sulfenyl chloride) **11d** and ethane-1,2-dithiol) gave the corresponding 1,2,4,5-tetrathianes such as **12d**, reasonably via the intermediacy of the corresponding thiosulfine **5d**:





(4)

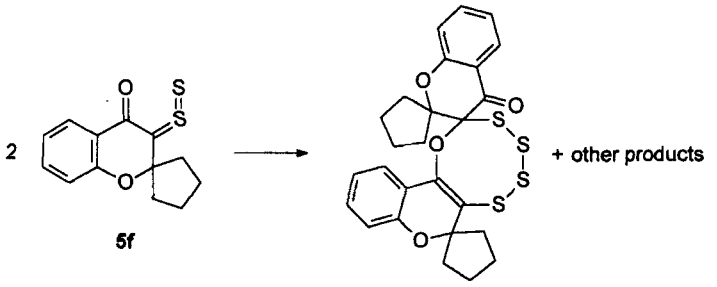
Also, several other derivatives of **11d** enter into reactions which lead to mixtures of the corresponding 1,2,4,5-tetrathiane **12d** and the corresponding 1,2,4-trithiolane **13d**, again strongly indicative of the intermediacy of **5d**. An especially intriguing and unexpected reaction took place between dimethyl 2,2-bis(acetyldithio)propanedioate **14** and SO_2Cl_2, an attempt to prepare dimethyl 2,2-bis(chlorodithio)propanedioate, $(MeOOC)_2C(SSCl)_2$ **15d**; see Sections 2.3, 2.5 and 4.7. It appears as if the corresponding thiocarbonyl *S*-disulfide **9d** is formed in an obscure first reaction step. This subsequently dimerizes to tetramethyl 1,2,3,5,6,7-hexathiocane-4,4,8,8-tetracarboxylate **16d** which, in turn, depending on the molar ratios of the reactants, the temperature and the reaction time, is partially degraded to dimethyl hexathiepane-7,7-dicarboxylate **17d** and dimethyl tetrathiolane-5,5-dicarboxylate **18d** by the SO_2Cl_2 present [27]:



(5)

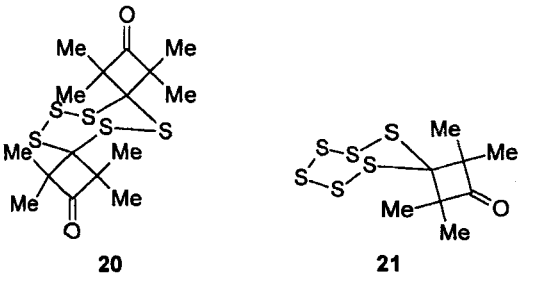
The unzipping of a series of acetyl α-chloroalkyl disulfides with morpholine led mainly to mixtures of *cis*- and *trans*-3,3,5,5-substituted 1,2,4-trithiolanes **13**, presumably formed from the corresponding thiosulfines **5** and thiones **8** [28].

An unprecedented [5 + 3] cycloaddition was observed in the dimerization of, *inter alia*, the α-oxo thiosulfine **5f** to the oxatetrathiocene **19** [29]:



5f **19**

Particularly fascinating recent experimental findings show the formation of the sulfur-rich heterocycles **20** and **21**, (see Scheme 2) from cyclobutane-derived dithiirane/thiosulfine tautomers by a mechanism apparently involving *both* the dithiirane (as sulfur acceptor) and the thiosulfine (as sulfur donor) [30].



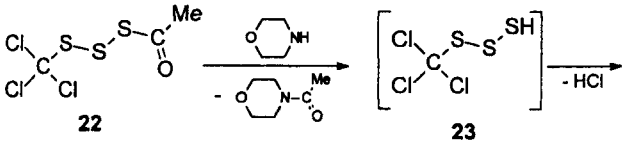
20 **21**

SCHEME 2

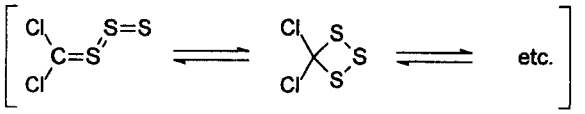
The thiation of thiophosgene **8a** with S_8 leads to products suggesting the intermediacy of, *inter alia*, thiophosgene *S*-sulfide (dichlorothiosulfine) **5a**; cf. Section 7.

2.2. Trithietanes–Thiocarbonyl *S*-Disulfides

Our first attempts to target this system (for simplicity, the theoretically possible isomeric dithiirane 1-sulfides, which do not seem to play any practical role, will be omitted everywhere in this discussion) simply extended our 'unzipping' of acetyl α-chloroalkyl disulfides with morpholine (to generate the corresponding S_2 system **9–24**) to the corresponding trisulfanes **22**:



22 **23**



9a **24a**

However, this concept failed to generate isolable S_3 products clearly derived from this equilibrium [31,32].

Later work by others and ourselves (cf. Section 2.1. and equation (3)) showed that thiocarbonyl *S*-disulfides **9** are readily formed by disproportionation of thiosulfines **5**. In all these instances subsequent cyclization reactions prevented any direct observation of **9**. Also other, more obscure, accesses to thiocarbonyl *S*-disulfides **9** have been found [27].

Trithietanes–thiocarbonyl *S*-disulfides are also intermediates in the mechanism proposed for the formation of **20** and **21** (cf. Scheme 2) [30].

The thiation of thiophosgene with S_8 leads to products suggesting the intermediacy of, *inter alia*, thiophosgene *S*-disulfide **9a**; cf. Section 7.

2.3. Tetrathiolanes

Dimethyl tetrathiolane-5,5-dicarboxylate **18d** is formed by chlorination of dimethyl 2,2-bis(acetyldithio)propanedioate **14d** with excess SO_2Cl_2 at elevated temperature (equation (5)). The identification of **18d**, which is formed via tetramethyl 1,2,3,5,6,7-hexathiocane-4,4,8,8-tetracarboxylate **16d**, and which could not be completely purified, rests mainly on spectroscopic evidence [27].

2.4. Pentathianes

Diethyl pentathiane-6,6-dicarboxylate **25e** was obtained, in admixture with several other compounds, on treatment of a $(EtOOC)_2C(SCl)_2$ **15e**–$(EtOOC)_2CClSCl$ **26e** mixture with CS; cf. Section 3 [33].

2.5. Hexathiepanes

Dimethyl hexathiepane-7,7-dicarboxylate **17d** is formed by chlorination of dimethyl 2,2-bis(acetyldithio)propanedioate **14d** with excess SO_2Cl_2 at room temperature; cf. Sections 2.3 and 4.8 and equation (5). Compound **17d** could, however, only be obtained in admixture with two unidentified compounds so that its identification rests on spectroscopic evidence only [27].

The spiro compound **21** was one of the products obtained from 3-(acetyldisulfanyl)-3-chloro-2,2,4,4-tetramethylcyclobutan-1-one **26h** by treatment with morpholine [30]. For details see Section 2.1.2.

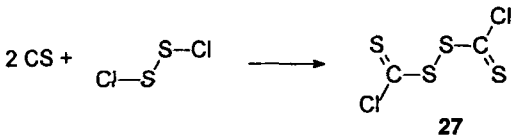
3. CARBON MONOSULFIDE [34,35]

The basis for this work was laid by Kenneth J. Klabunde (Kansas State University, Manhattan, KS, USA) who about 30 years ago developed a practical way to generate carbon monosulfide on a preparative scale and used it to study reactions of CS with inorganic compounds [36]. In 1984 a most productive cooperation between our two groups was initiated with the aim to study CS as a reagent in organic synthesis. Later, also Adolf Krebs (University of Hamburg, Germany) participated in the project which led to additional exciting findings.

Carbon monosulfide is a highly reactive gas which must be handled in a vacuum line and behaves by and large like isocyanides, but unlike isocyanides it polymerizes rapidly in the absence of reactive reaction partners. Thus, potential slow reactions (which pose no problem in the case of isocyanides) cannot be observed since they cannot compete with the CS → $(CS)_n$ process [34,35]. Another limitation concerns working temperatures below *ca.* −100 °C because solid CS can be frozen out which, on reheating, may polymerize to $(CS)_n$ with explosive force. The reactivity of carbon monosulfide towards organic substrates (*vide infra*) was subjected to quantum chemical analysis with the main conclusion that CS can be regarded as a σ-donor as well as as a π-acceptor [37].

In a painstaking investigation of the mechanism of the electrochemical reduction of carbon disulfide it could be shown that contrary to earlier literature claims (a) CS is not formed during the electrochemical reduction of CS_2, (b) CS does not react with sodium trithiocarbonate and (c) CS does not react with tetraethylammonium tetrathiooxalate [38].

3.1. Reactions with Sulfenyl Chlorides



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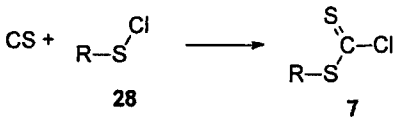

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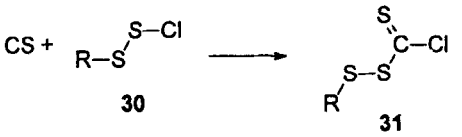
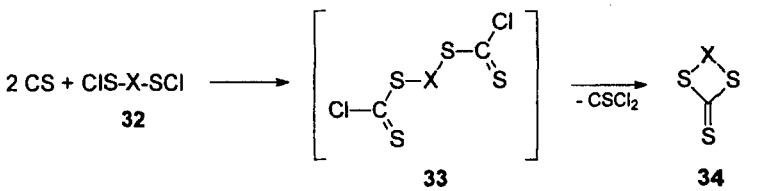


(10)



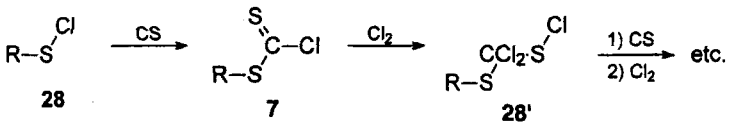
(11)

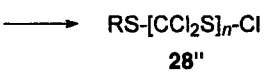
SCHEME 3

As shown in Scheme 3 the first successful experiment in our CS work was the insertion of CS into the S–Cl bonds of S_2Cl_2 to yield bis(chlorothiocarbonyl) disulfide **27**; cf. equation (8) [39]. The scope of this very neat reaction was later extended to sulfenyl

chlorides **28** and thiosulfenyl chlorides **30**; cf. equations (9) and (10) [37,40–45]. It was found that acetyl chlorothiocarbonyl sulfide, MeCOSCSCl **29**, whether prepared from acetylsulfenyl chloride, MeCOSCl, and CS or from thioacetic acid, MeCOSH, and thiophosgene **8a**, spontaneously decomposes to acetyl chloride and CS_2 [42]. In the case of bis(sulfenyl chlorides) **32** we observed that the bis(chlorodithioformates) **33** (also accessible from α,ω-dithiols and thiophosgene **8a**) are in general inherently unstable and rapidly form cyclic trithiocarbonates **34** with presumable loss of thiophosgene **8a**; cf. equation (11). An exception to this general rule are the bis(sulfenyl chlorides) 1,1,2,2-tetrafluoroethane-1,2-disulfenyl dichloride **32a** and 1,3,4-thiadiazole-2,5-disulfenyl dichloride **32b** which do form isolable diinsertion products with CS. In the former case the cyclic trithiocarbonate **34** is disfavored by the mutual repulsion of eclipsing fluorine atoms, in the latter by prohibitive ring strain [44]. *gem*-Disulfenyl dichlorides **11** diinsert CS without subsequent loss of thiophosgene [33].

Since chlorodithioformates **7** can be chlorinated to sulfenyl chlorides **28**, (see Sections 7.5 and 8.2), which in turn can be converted to new chlorodithioformates **7** by treatment with CS, one could think of constructing a formal oligomer of thiophosgene **8a** (with the end groups shown) from 1 mol of a sulfenyl chloride **28** and n mol of CS by a sequence of such reaction steps:



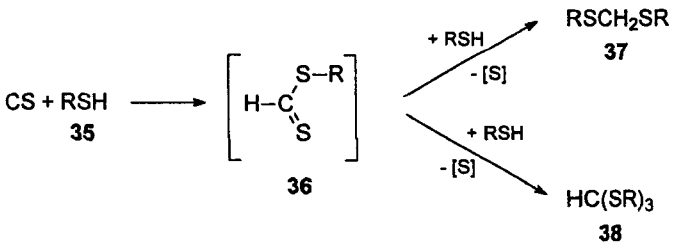


(12)

However, rapidly diminishing yields make this approach impractical [46].

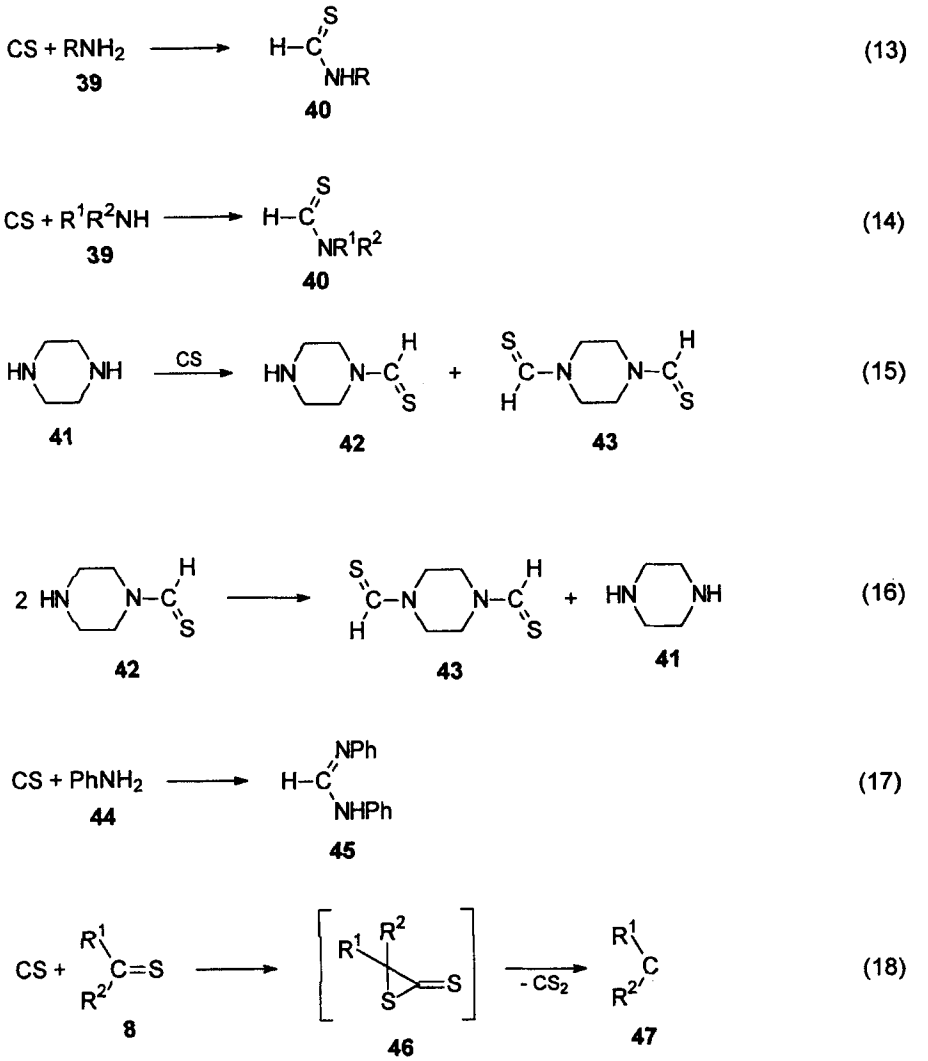
3.2. Reactions with Thiols

The primary reaction between CS and thiols **35** is insertion into the S–H bond with formation of a labile dithioformate **36**. Secondary reactions between **36** and the starting thiol **35** then lead to formaldehyde dithioacetals **37** and/or trithioorthoformates **38**; cf. Scheme 4 [37,47].



SCHEME 4

3.3. Reactions with Amines

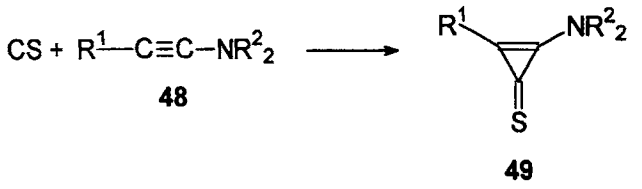


SCHEME 5

As shown in Scheme 5 insertion into the N–H bond is observed when primary or secondary amines **39** are treated with CS, the latter being markedly more reactive; cf. equations (13) and (14). In the case of piperazine **41** both the *N*-thioformyl **42** and the *N*,*N*′-bis(thioformyl) derivative **43** could be obtained; cf. equation (15) [37,47]. In a later study we could show that **42** readily disproportionates to **43** and piperazine **41**; cf. equation (16) [48]. Carbon monosulfide converts aniline **44** to *N*,*N*′-diphenylformamidine **45**, a somewhat unexpected reaction; cf. equation (17). Unfortunately, this peculiar reaction could not be generalized to the generation, under extremely mild conditions, of carbenes **47** by desulfuration of thiocarbonyl compounds **8** with CS via ring-strained α-dithiolactones **46**; cf. equation (18) [46].

3.4. Reactions with Ynamines

A very neat [1+2] cycloaddition leading to cyclopropenethiones **49** takes place when CS is allowed to react with ynamines (alk-1-yn-1-amines) **48**:

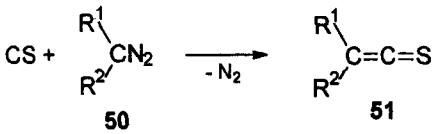


48 **49** (19)

No corresponding reactions are seen with other electron-rich alkynes such as 1-alkoxyalk-1-ynes, 1-alkylthioalk-1-ynes and 1-alkylselenoalk-1-ynes and with ring-strained cycloalkynes [37,49].

3.5. Reactions with Diazoalkanes

We found that isolable, sterically hindered thioketenes **51** can be prepared from CS and the corresponding diazoalkanes **50**:



50 **51** (20)

When one tries to synthesize reactive thioketenes from diazoalkanes and CS the system becomes uncontrollable because of secondary reactions between the thioketene and the starting diazoalkane. Resonance-stabilized diazoalkanes such as diazomalonates do not react with CS [37,50].

4. SULFENIC ACID DERIVATIVES

Concerning new thiophenesulfenyl chlorides used as intermediates in a thiophene project, see Section 9.1. The elusive 1,2,2-triphenylethene-1-sulfenyl chloride **52** could be prepared in solution by chlorination of the known 1,2,2-triphenylethene-1-thiol and, *inter alia*, characterized by derivatization with thioacetic acid (to the corresponding unsymmetrical disulfide) and with morpholine (to the corresponding sulfenamide). On attempted isolation **52** cyclizes, with loss of HCl, to 2,3-diphenylbenzo[*b*]thiophene [51]. Similar observations were made in the chlorination of tetrazole-5-thiol. The corresponding sulfenyl chloride can be kept in solution for a short time and derivatized but not isolated [52].

Highly functionalized sulfenyl chlorides $ArSCCl_2SCl$ **53** could be obtained by chlorination of aryl chlorodithioformates **7** [53]. The corresponding reaction of *C*-sulfonyldithioformates **54** leads to $R^1SO_2(R^2S)CClSCl$ **55** [54,55]. The latter can, depending on the substitution pattern and the reaction conditions, rearrange to the disulfide $R^1SO_2CCl_2SSR^2$ **56** or to the thiosulfonate $R^1SO_2SCCl_2SR^2$ **57** [56].

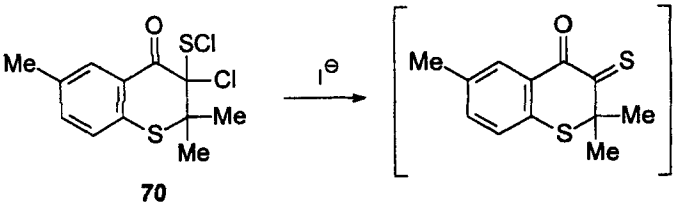
An attempt to prepare 1-acetyl-2-(4-morpholino)disulfane **58** showed that **58** readily disproportionates to the corresponding sulfane **59** and trisulfane **60** and that **58**, **59** and **60** all suffer spontaneous loss of sulfur to form acetomorpholide [57].

The thiolsulfonate $PhSO_2SCH(SO_2Ph)_2$ **61** with its exceptionally good carbon-centered leaving group on S(II) behaves like the hypothetical sulfenyl chloride $PhSO_2SCl$ **62**, i.e. it forms $PhSO_2SN(CH_2CH_2)_2O$ **63** with morpholine [58]. On the other hand, **61** sulfenylates active methylene compounds generating the corresponding *C*-[bis(phenylsulfonyl)methylthio] derivatives [59].

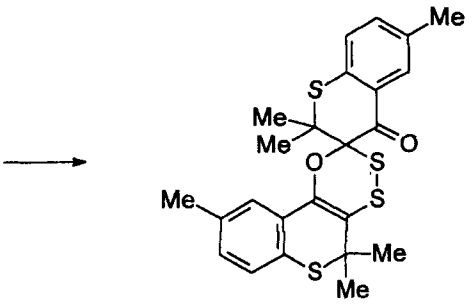
2-Chloro-1,3-dioxo-1,3-diphenylpropane-2-sulfenyl chloride $(PhCO)_2CClSCl$ **64**, unavailable from 1,3-diphenylpropane-1,3-dione (dibenzoylmethane) **65** and $SOCl_2$ (cf. Section 8.1), could be prepared by chlorination of the disulfide $(PhCO)_2CHSSCH(COPh)_2$ **66**, made from copper(II) bis(1,3-dioxo-1,3-diphenylpropan-2-ide) **67** and S_2Cl_2 [60].

Sulfenyl chlorides RSCl **28** and thiosulfenyl chlorides RSSCl **30** add to thiophosgene **8a** with formation of the corresponding trichloromethyl compounds $RSSCCl_3$ **68** and $RSSSCCl_3$ **69** respectively [61].

β-Oxo *α*-chloro sulfenyl chlorides such as **70** on treatment with iodide ions form the corresponding thiones (rather than the expected disulfides) which subsequently dimerize in a Diels–Alder fashion [62,63]:



70



71

(21)

4.1. Trichloromethanesulfenyl Chloride

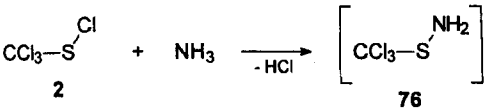
This commercially available highly functionalized C_1 compound **2** is prepared by chlorination of carbon disulfide in the presence of iodine (chlorination of carbon disulfide in the presence of iron yields carbon tetrachloride and SCl_2) and has a challenging chemistry. Much of the attention it has received derives from the commercial success of the fungicide captan (3a,4,7,7a-tetrahydro-2-[(trichloromethyl)thio]-1*H*-isoindole-1,3(2*H*)-dione) [64] which was prepared from it [65]. On careful analysis of commercial

2 we discovered that it contains the previously unobserved contaminant dichloromethanedisulfenyl dichloride, $CCl_2(SCl)_2$, **11a**, the product of the photochlorination of carbon disulfide [66].

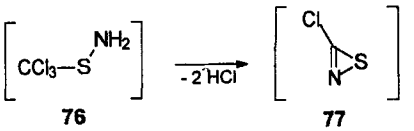
One of our earliest experiments in this area was the preparation of distillable trichloromethanesulfenyl thiocyanate, CCl_3SSCN, **72** (from **2** and potassium thiocyanate), a structurally close relative of the pseudohalogen thiocyanogen, NCSSCN, **73** [67]. However, **72** did not exhibit any halogen-like behavior [46].

4.1.1. The Reaction of Trichloromethanesulfenyl Chloride with Ammonia

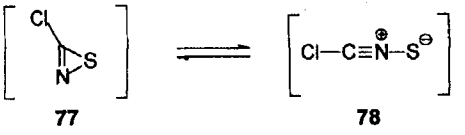
At a time when a plethora of nitrogen-containing compounds, especially imides, had been treated with trichloromethanesulfenyl chloride **2** to yield analogs of captan (cf. Section 4.1), the seemingly simple reaction with ammonia had not been investigated yet. We decided to do just that and obtained what we thought was a dimeric product $(CClNS)_2$ to which we assigned the structure of 3,6-dichloro-1,4,2,5-dithiadiazine **74** [68]. The subsequent observation that this heterocycle on thermolysis failed to yield the known aromatic 3,5-dichloro-1,2,4-thiadiazole suggested a reexamination of this structure. Mass spectrometry, which had just become available at this time, showed that the compound was in fact a tetramer $(CClNS)_4$ [69] and a single-crystal X-ray study revealed its structure as 2,3,7,8-tetrachloro-5,10,11,12-tetrathia-1,4,6,9-tetraazatricyclo[5.3.1.1^{2,6}]dodeca-3,8-diene **75** [70,71].



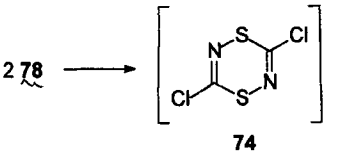
(22)



(23)



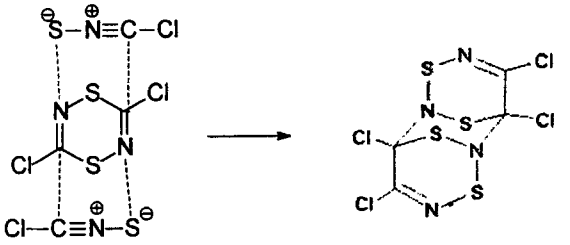
(24)



(25)

SCHEME 6

As shown in Scheme 6 the key intermediates appear to be 3-chlorothiazirine **77** and chloromethanenitrile *N*-sulfide (cyanogen chloride *N*-sulfide) **78**; cf. equations (22)–(24). The latter dimerizes head-to-tail to 3,6-dichloro-1,4,2,5-dithiadiazine **74**, equation (25), which then in turn adds another two molecules of **78** in a quasi-head-to-head fashion to yield the tricyclic tetramer **75**:



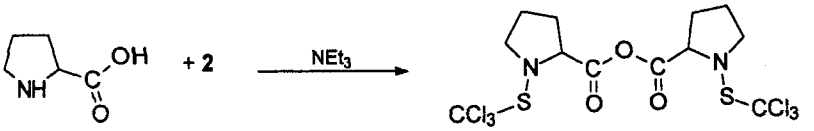
75 (26)

It is hard to imagine this process other than as a third-order reaction where a mind-boggling eight reaction centers interact simultaneously and in a highly ordered fashion (no less intricate would be a scenario where two molecules of **74** dimerized to an adduct which subsequently rearranged to **75**). Attempts to harvest larger amounts of **75** from this low yielding reaction were foiled by an apparently inverse relationship between reaction scale and yield [69]. Attempts to extend this reaction to related compounds such as tribromomethanesulfenyl bromide, CBr_3SBr, **79** failed.

4.1.2. Reactions of Trichloromethanesulfenyl Chloride with Secondary and Tertiary Amines

As was the case in Section 4.1.1, the reactions described in this section all had one kind of twist or another and yielded a number of unconventional products which would have been difficult to prepare by design.

4.1.2.1. The Reaction with L-Proline Treatment of L-proline **80** with **2** in the presence of triethylamine leads to 1-[(trichloromethyl)thio]-L-proline anhydride **81**:

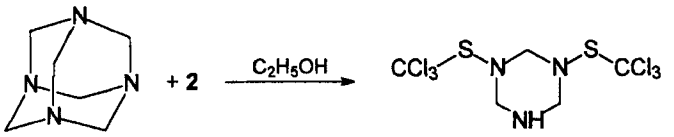


80 **81** (27)

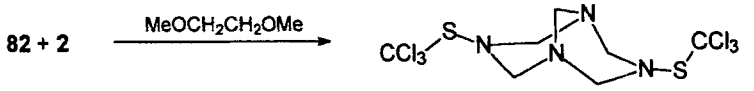
L-4-Hydroxyproline does not react with **2** under these conditions [72]. No efforts were made to elucidate the mechanism of this somewhat unexpected reaction.

4.1.2.2. Reactions with Hexamethylenetetramine It is known that 1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane (hexamethylenetetramine) **82** reacts with electrophiles to yield

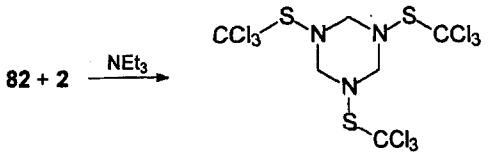
N-persubstituted hexahydro-1,3,5-triazines and/or 1,3,5,7-tetraazabicyclo[3.3.1]-nonanes. As shown in Scheme 7 when **2** was allowed to react with **82** in ethanol 1,3-bis [(trichloromethyl)thio]hexahydro-1,3,5-triazine **83** was obtained in a somewhat unexpected course of events; cf. equation (28). Interestingly, 2-nitrobenzenesulfenyl chloride did not yield an analogous product with **82**. On the other hand, the corresponding reaction with 1,2-dimethoxyethane as the solvent gave 3,7-bis[(trichloromethyl)-thio]-1,3,5,7-tetraazabicyclo[3.3.1]nonane **84**; cf. equation (29). The above-mentioned disubstituted hexahydro-1,3,5-triazine **83** could be further substituted in the 5-position which, *inter alia*, gave access to 1,3,5-tris[(trichloromethyl]thio]hexahydro-1,3,5-triazine **85**, cf. equation (30) [73].



82 **83** (28)



84 (29)

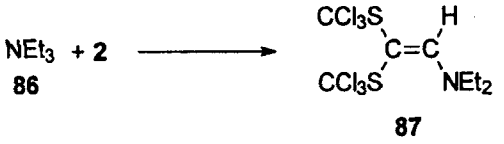


85 (30)

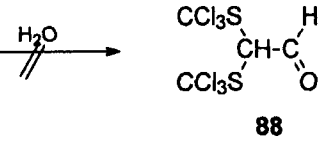
SCHEME 7

4.1.2.3. The Reaction with Triethylamine After triethylamine **86** had been routinely and successfully used as an otherwise inert HCl scavenger in a large number of sulfenylations with **2** we were surprised by the observation that, in the absence of more reactive substrates, **86** reacts with **2**; see Scheme 8. After a long sequence of chlorinations, dehydrochlorinations and additions of **2** to intermediate vinylamines the final product is 1,1-bis[(trichloromethyl)thio]-2-(*N*,*N*-diethylamino)ethene **87**; cf. equation (31) [74]. Its structure was determined by single-crystal X-ray crystallography [75]. A detailed description of the individual reaction steps can be found in our cited paper. In support of the suggested reaction mechanism it could be shown that **87** is also formed in the system *N*,*N*-diethylethenamine (diethylvinylamine)–trimethylamine–**2**. Although formally an enamine **87** does not show any of the typical enamine reactions, i.e. its C=C double bond is electrophilic rather than nucleophilic. Thus, the parent

2,2-bis[(trichloromethyl)thio]ethanal **88** could not be obtained by controlled hydrolysis; cf. equation (32) [74].



(31)

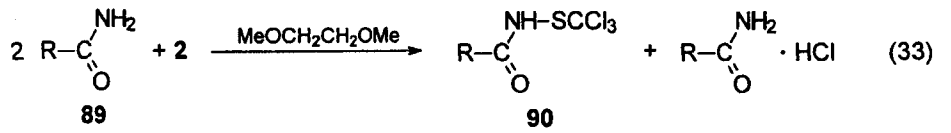


(32)

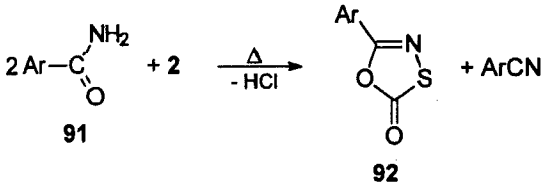
SCHEME 8

4.1.3. Reactions of Trichloromethanesulfenyl Chloride with Amides and Hydrazides

Our attempts to *N*-sulfenylate simple aliphatic amides **89** with **2** were unsuccessful until we discovered that 1,2-dimethoxyethane was the solvent of choice and that no extraneous base was required. The somewhat counterintuitive fact that **89** form stable hydrochlorides allowed the starting amide **89** to serve as HCl scavenger; see Scheme 9, equation (33) [76]. The same method could also be used with acid hydrazides [77]. With benzamide **91a** no reaction was observed unless the reaction mixture was heated and then 5-phenyl-1,3,4-oxathiazol-2-one **92a** was formed, probably by hydrolysis of the intermediate *N*-[(trichloromethyl)thio]benzamide **93** to *N*-[(chlorocarbonyl)thio]benzamide **94** (with concomitant dehydration of an equivalent amount of amide to nitrile) which then cyclizes with elimination of HCl; cf. equation (34) [78,79].



(33)



(34)

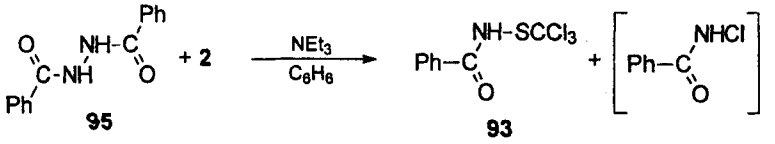
a, Ar = Ph
b, Ar = 4-(CH_2Cl)C_6H_4

SCHEME 9

A large number of 5-aryl-1,3,4-oxathiazol-2-ones **92** were obtained in this way while the analogous preparation of 5-alkyl-1,3,4-oxathiazol-2-ones required the addition of

an equivalent amount of benzamide because the starting alkanamides apparently were unsuitable as the source of water for the required hydrolysis [79]. More about 5-substituted 1,3,4-oxathiazol-2-ones **92** is given in Section 9.2.

Interestingly, *N*-[(trichloromethyl)thio]benzamide **93** which could not be obtained from benzamide **91** (Ar = Ph) and **2** (*vide supra*), was formed on trichloromethanesulfenylation of *N*,*N*-dibenzoylhydrazine **95** [77]:



(35)

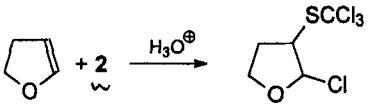
4.1.4. Reactions of Trichloromethanesulfenyl Chloride with Activated Aromatic Compounds

In our quest for trichloromethyl sulfides **1** (cf. Section 1), we also reinvestigated the known *p*-trichloromethanesulfenylation of (*N*,*N*-dialkylamino)arenes **96** with trichloromethanesulfenyl chloride **2** [5]. Our conclusions could only add little to what was already known. Typical Friedel–Crafts catalysts were either too unreactive to improve the synthetic scope or too reactive in the sense that they led to the, likewise known, formation of crystal violet type dyes rather than of **1**. With regard to the starting arenes **96** substitution *ortho* to the *N*,*N*-dialkylamino group (regardless of the nature of the substituent) prevents the sulfenylation in the *p*-position, most probably by exclusion of the necessary coplanarity of the *N*,*N*-dialkylamino group with the benzene ring. Corresponding *meta* substitution is permissible as long as the substituent is first order.

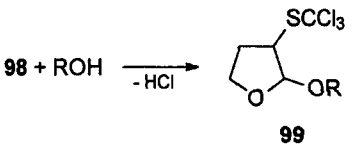
4.1.5. The Addition of Trichloromethanesulfenyl Chloride to Multiple Bonds

Trichloromethanesulfenyl chloride **2** belongs to the least reactive sulfenyl chlorides and thus does not readily add to unactivated C=C double bonds. In the cases described in Sections 4.1.5.1 and 4.1.5.2 the multiple carbon–carbon bonds are appropriately activated by donor substituents.

4.1.5.1. Addition to C=C Double Bonds 2,3-Dihydrofuran **97** is a readily available, highly reactive alkene which, with hydrochloric acid catalysis, adds **2** practically instantaneously, see Scheme 10, equation (36). Treatment of the addition product **98** with alcohols leads to the corresponding 2-alkoxytetrahydrofurans **99**; cf. equation (37). The stereochemistry of these addition and substitution products was not investigated [80,81].



(36)

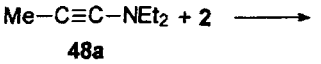


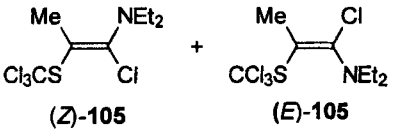
(37)

SCHEME 10

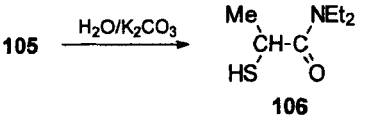
The adduct of **2** to cyclohexene, i.e. 2-chlorocyclohex-1-yl trichloromethyl sulfide **100**, can be partially hydrolyzed to yield *S*-(2-chlorocyclohex-1-yl) chlorothioformate **101** [82]. On the other hand, trichloromethyl thiocyanate, CCl_3SCN, **102** is hydrolyzed to *S*-(trichloromethyl) thiocarbamate, CCl_3SCONH_2, **103** while the corresponding *N*-alkyl derivatives **104** are accessible under Ritter conditions [83].

4.1.5.2. Addition to C≡C Triple Bonds The addition of **2** to the C≡C triple bond of *N*,*N*-diethylpropyn-1-amine **48a** proceeds smoothly to yield 1-chloro-*N*,*N*-diethyl-2-[(trichloromethyl)thio]-1-propen-1-amine **105** as a mixture of (*E*)- and (*Z*)-isomers; see Scheme 11 and equation (38). Hydrolysis of this isomer mixture with water in the presence of potassium carbonate yields, somewhat surprisingly, (*R*,*S*)-*N*,*N*-diethyl-2-mercaptopropanamide **106**, cf. equation (39) [84].





(38)

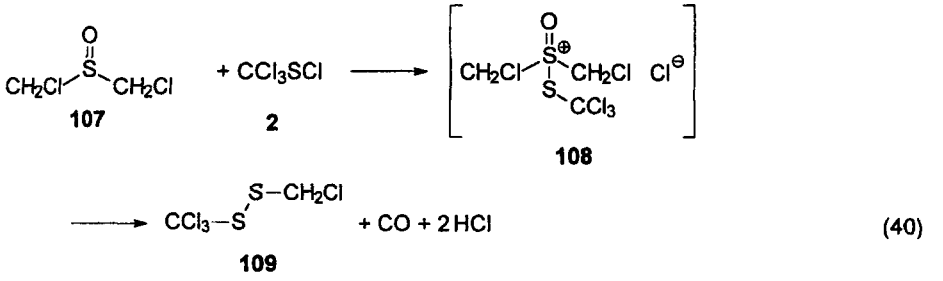


(39)

SCHEME 11

4.1.6. Reactions of Trichloromethanesulfenyl Chloride with Aliphatic Sulfoxides

The intriguing anti-Pummerer reaction

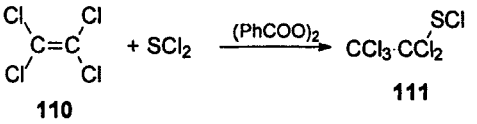


(40)

which takes place between **2** (and similar sulfenyl chlorides) and aliphatic sulfoxides can be applied to the preparation of elusive unsymmetrical disulfides such as **109** [85,86]. In the case shown bis(chloromethyl) sulfoxide **107** becomes the synthetic equivalent of the non-existent chloromethanethiol.

4.2. Pentachloroethanesulfenyl Chloride

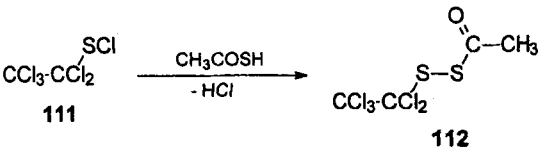
According to an obscure patent pentachloroethanesulfenyl chloride **111** can be conveniently prepared by benzoyl peroxide catalyzed addition of SCl_2 to tetrachloroethene **110** [87]:



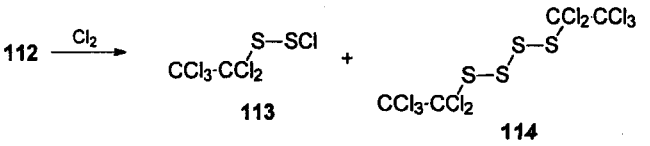
110 **111** (41)

This ready accessibility greatly facilitated our study of its most interesting chemistry. Attempts to prepare an analogous sulfenyl chloride from hexachloropropene in the same way failed, most likely because of extreme steric hindrance [46].

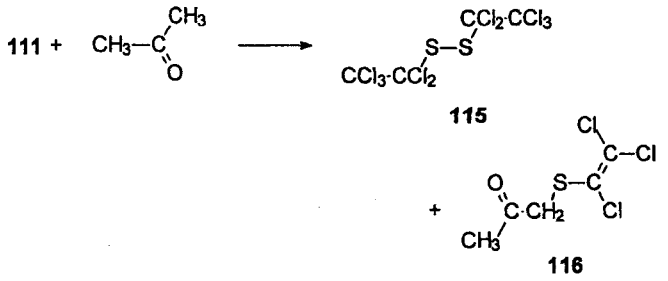
4.2.1. Pentachloroethanethiosulfenyl Chloride and Bis(pentachloroethyl)oligosulfanes



111 **112** (42)



113 **114** (43)



115 **116** (44)

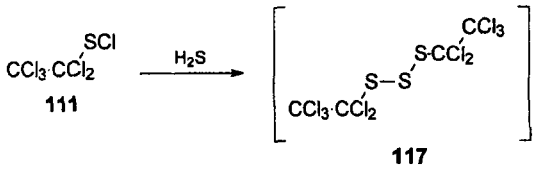
SCHEME 12

As shown in Scheme 12 pentachloroethanesulfenyl chloride **111** reacts smoothly with thioacetic acid to form the mixed disulfide **112** (cf. equation (42)) which in turn can be cleaved with chlorine to yield pentachloroethanethiosulfenyl chloride [chloro(pentachloroethyl)disulfane] **113** (cf. Sections 4.7 and 4.8), accompanied by a substantial amount of bis(pentachloroethyl)tetrasulfane **114**; cf. equation (43) [87,88]. This chlorodisulfane which had been described previously, but without a rational

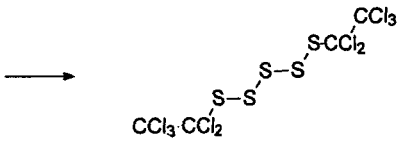
synthesis, proved extremely useful in our efforts to obtain stable derivatives of trithiocarbonic acid; cf. Section 7.1.

The reaction between pentachloroethanesulfenyl chloride **111** and excess acetone at room temperature (reaction time 11 days) yielded unexpectedly bis(pentachloroethyl) disulfide **115** and 1-[(trichloroethenyl)thio]propan-2-one **116**; cf. equation (44) [88].

When pentachloroethanesulfenyl chloride **111** was treated with hydrogen sulfide none of the expected trisulfane **117** was observed, but only bis(pentachloroethyl)pentasulfane **118** could be isolated [89]:



111 **117**

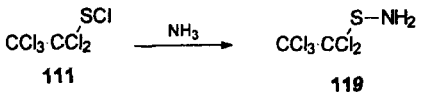


118 (45)

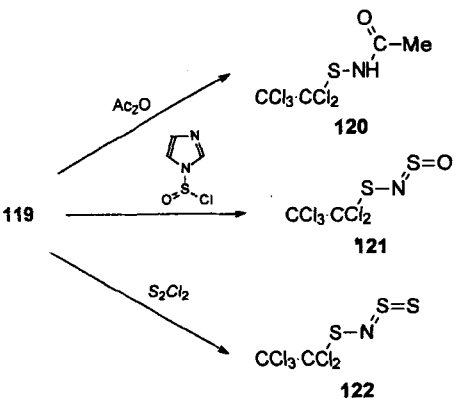
While it stands to reason that the pentasulfane **118** is formed by disproportionation of the corresponding, still unknown, trisulfane **117** no other disproportionation products could be observed.

Thus, in the oligosulfane series $CCl_3CCl_2S_nCCl_2CCl_3$ the compounds with $n=2$, 4, 5 have by now been prepared while their congeners with $n=1$, 3 have never been encountered.

4.2.2. Pentachloroethanesulfenamides



111 **119** (46)



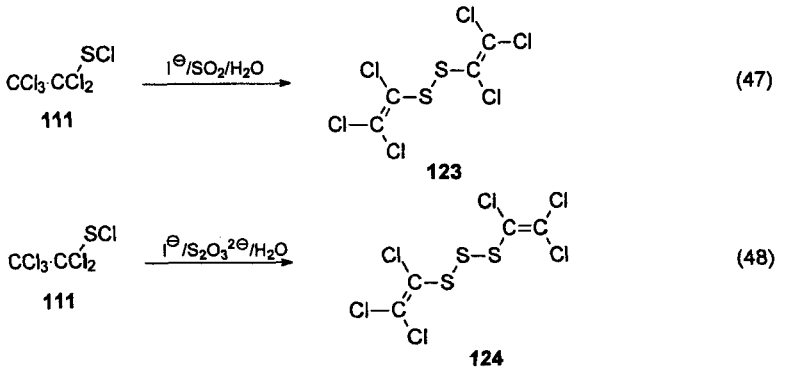
120 **121** **122**

SCHEME 13

Contrary to chemical intuition pentachloroethanesulfenamide **119** proved very easy to prepare (from pentachloroethanesulfenyl chloride **111** and gaseous ammonia) (see Scheme 13 and equation (46)) and to be surprisingly stable and well behaved, except for its failure to be purifiable by recrystallization or sublimation. Derivatization with acetic anhydride, *N*-(chlorosulfinyl)imidazole and S_2Cl_2 led to the equally well-behaved derivatives **120**, **121** and **122**, respectively; cf. Scheme 13 [90].

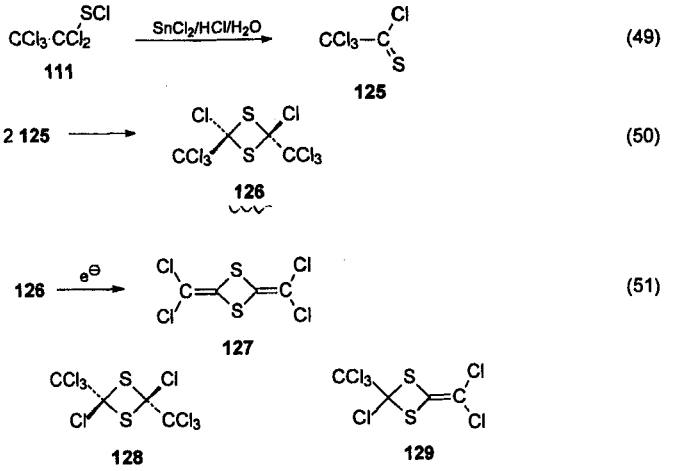
With a number of primary and secondary amines pentachloroethanesulfenyl chloride **111** forms the corresponding sulfenamides. The former products can be further *N*-acylated [91].

4.2.3. The Reduction of Pentachloroethanesulfenyl Chloride



SCHEME 14

Under conditions where trichloromethanesulfenyl chloride **2** is reduced to thiophosgene **8a** pentachloroethanesulfenyl chloride **111** can behave quite differently. As shown in Scheme 14 with I^-–SO_2–H_2O it forms bis(trichloroethenyl) disulfide **123** and with I^-–$S_2O_3^{2-}$–H_2O bis(trichloroethenyl)trisulfane **124**; cf. Scheme 14, equations (47) and (48) [89].



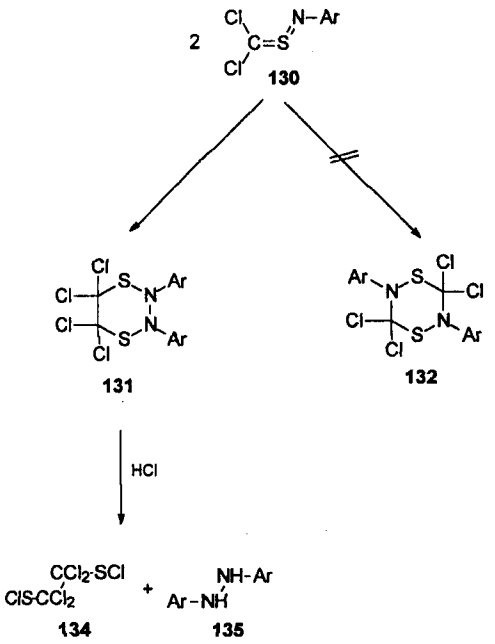
SCHEME 15

The CCl_3SCl **2**–$CSCl_2$ **8a** analogy was, however, valid when tin(II) chloride in concentrated hydrochloric acid was employed as reducing agent (see Scheme 15). In a very neat reaction the intensely purple-colored trichlorothioacetyl chloride **125** is formed; cf. equation (49). This thioacyl chloride rapidly dimerizes to the colorless *trans*-2,4-bis(trichloromethyl)-2,4-dichloro-1,3-dithietane **126;** cf. equation (50) [92]. The structure of **126** was elucidated by single-crystal X-ray crystallography [93]. Electrochemical reduction of **126** (this work was carried out in collaboration with Torben Lund, now at Roskilde University, Denmark) leads to 2,4-bis(dichloromethylene)-1,3-dithietane **127**, the formal head-to-tail dimer of 2,2-dichloroethenethione (dichlorothioketene) **51a** [94]; cf. equation (51) and Section 7.6.1. Interestingly, a large number of attempts to convert **126** to **127** by wet chemical reduction failed [46].

During these studies the *cis*-isomer **128** and the half-reduced compound **129** remained unobserved.

4.3. 1,1,2,2-Tetrachloroethane-1,2-disulfenyl Dichloride

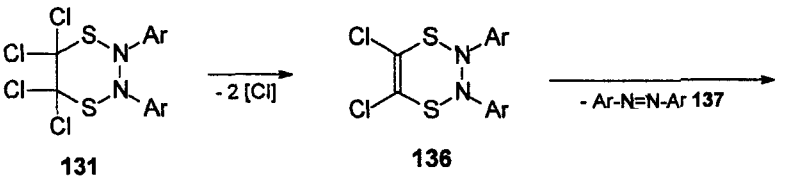
When Potts and Baum discovered that thiophosgene *S*-(*N*-arylimines) **130** do not dimerize head-to-tail, i.e. to **132**, as claimed in the older literature, but rather head-to-head, i.e. to **131** [95], it occurred to us that the puzzling claim of the formation of distillable trichloromethanethiol, CCl_3SH, **133** by treatment of these dimers with gaseous HCl [96] must be in error and that the product in question might be 1,1,2,2-tetrachloroethane-1,2-disulfenyl dichloride **134**. We were indeed able to prove this point and to characterize **134** to modern standards; see Scheme 16 [97].



SCHEME 16

Unfortunately, all attempts to convert **134** or its precursors to dithiooxalyl chloride **138** and/or its isomer 3,4-dichloro-1,2-dithiete **139**, long-sought targets of our

endeavors in sulfur chemistry, remained unsuccessful. Among many other attempts the dechlorination of **131** to **136** was unpredictable and the subsequent retro-Diels–Alder reaction did give some azoarene **137**, but none of the **138** ⇌ **139** equilibrium mixture [46]:

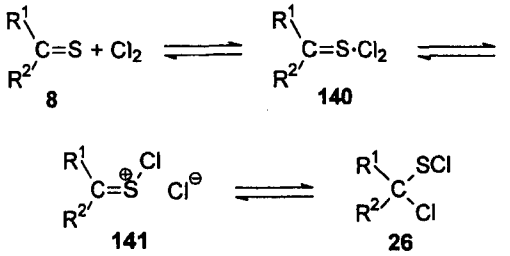


131 **136**

138 **139** (52)

4.4. Cyclobutanesulfenyl Chlorides

Thiocarbonyl compounds react with chlorine in various ways. In three, basically reversible, steps the reaction partners can form a lose π-complex **140**, an ionic σ-complex **141** and, finally, an α-chloro sulfenyl chloride **26** with covalent bonds [98]:

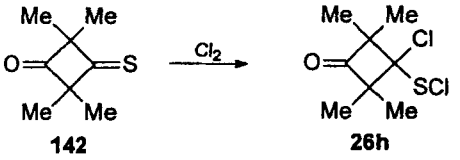


8 **140**

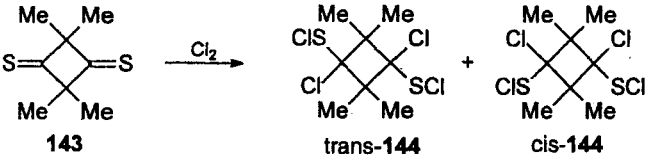
141 **26** (53)

The extent to which this sequence of events proceeds to the right will be crucially dependent on the nature of the substituents R^1 and R^2. If R^1 and R^2 are simple alkyl or aryl groups they will stabilize the positive charge in the σ-complex **141** to a degree which will prevent the formation of the α-chloro sulfenyl chloride **26**. Thus, neither di-*tert*-butyl thioketone nor thiobenzophenone forms stable α-chloro sulfenyl chlorides on chlorination [46]. By the same token electron-withdrawing substituents R^1 and R^2 will destabilize the σ-complex **141** and thus favor the formation of the α-chloro sulfenyl chloride **26**. Another factor which can stabilize an α-chloro sulfenyl chloride **26** vis-à-vis the σ-complex **141** is the rehybridization of an sp^2 thiocarbonyl carbon atom in an angle-strained small ring to an sp^3-hybridized α-chloro sulfenyl chloride carbon atom. We were, in collaboration with Grzegorz Mloston (University of Łodz, Poland), able to demonstrate this effect in the chlorination of

the cyclobutanethiones **142** and **143** which yielded the isolable α-chloro sulfenyl chlorides **26h** and **144**, respectively; see Scheme 17, equations (54) and (55) [99].



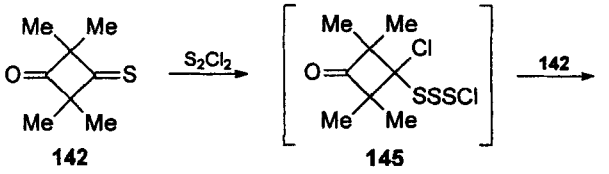
(54)

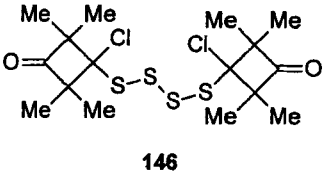


(55)

SCHEME 17

The sulfenyl chloride **26h** and the thiosulfenyl chloride **152h** (available from 2,2,4,4-tetramethyl-3-thioxocyclobutan-1-one **142** and SCl_2) smoothly add to nonenethiolizable thioketones to yield the corresponding unsymmetrical disulfides and trisulfanes, respectively. With S_2Cl_2 2,2,4,4-tetramethyl-3-thioxocyclobutan-1-one **142** forms the corresponding symmetrical tetrasulfane **146**, by necessity via the corresponding chlorotrisulfane **145** which, however, could not be isolated or trapped [30]:





(56)

4.5. 2-Chloro-2-(chlorothio)propanedioic Acid Derivatives

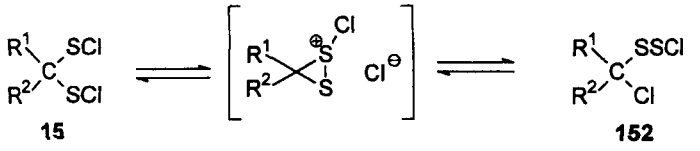
The title compounds $(RCO)_2CClSCl$ **26** were prepared by known chemistry (reaction of malonic acid derivatives with $SOCl_2$ in the presence of a catalytic amount of pyridine). From diethyl malonate we thus obtained the corresponding **26d** (R = EtOOC) which could be converted (with thioacetic acid) to the corresponding unsymmetrical disulfide

$(EtOOC)_2CClSSCOMe$ **147** which in turn could be chlorinated to a mixture of the expected thiosulfenyl chloride $(EtOOC)_2CClSSCl$ **26d** and the unexpected tetrasulfane $(EtOOC)_2CClSSSSCCl(COOEt)_2$ **148**. The reaction of **26d** with *tert*-butylamine led to the corresponding thiocarbonyl *S*-imide $(EtOOC)_2C{=}S{=}N\text{-}Bu\text{-}t$ **149** which, however, was too unstable to survive extensive purification steps (concerning stable thiocarbonyl *S*-imides, see Section 8.2) [45].

In an extension of this work we noted that the reaction of malonic acid derivatives with $SOCl_2$, in addition to $(RCO)_2CClSCl$ **26**, also yields the corresponding disulfides $(RCO)_2CClSSCCl(COR)_2$ **150** and/or trisulfanes $(RCO)_2CClSSSCCl(COR)_2$ **151** [100]. For reactions of **26** involving dithiirane–thiosulfine chemistry, see Section 2.1.2, for reactions with CS, see Section 2.5.

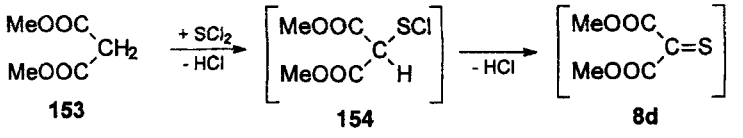
4.6. *gem*-Disulfenyl Dichlorides [101]

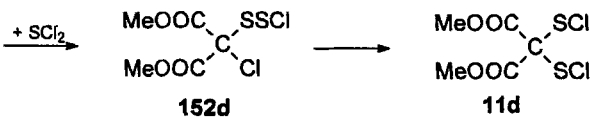
In the context of our interest in dithiiranes–thiosulfines (cf. Section 2.1), *gem*-disulfenyl dichlorides $R^1R^2C(SCl)_2$ **11** (typically obtained in admixture with the isomeric chloro(α-chloroalkyl)disulfanes $R^1R^2CClSSCl$ **152** with which they form a tautomeric equilibrium, cf. equation (57)) were of interest as potentially dechlorinatable precursors.



(57)

Compounds **11** are indeed *rarae aves*, the best known subspecies being **11a** ($R^1 = R^2 = Cl$) [102,101] and the malonic acid derivatives **11** ($R^1 = R^2 = RCO$) [101]. Prior to our investigations no **11** had been rigorously purified and characterized to the highest standards. This deficiency could be rectified when we succeeded in the preparation of the solid compound **11d** ($R^1 = R^2 = MeOOC$) which was amenable to recrystallization and subsequent single-crystal X-ray structure determination. We could also elucidate the mechanism of its formation from dimethyl malonate and SCl_2 [27]:





(58)

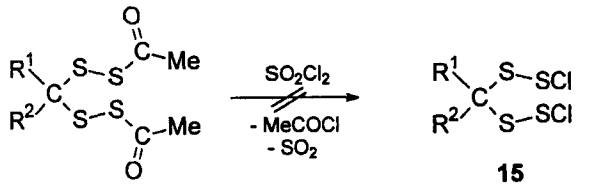
For reactions with CS, cf. Section 2.5.

4.7. Thiosulfenyl Chlorides (Alkyl- and Arylchlorodisulfanes)

Highly functionalized thiosulfenyl chlorides $ArSCCl_2SSCl$ **30** could be obtained by addition of SCl_2 to aryl chlorodithioformates **7** [53]. See also Section 4.2.1.

4.8. *gem*-Bis(thiosulfenyl chlorides)

We were unable to obtain the title compounds **15** by chlorination of the corresponding *gem*-bis(acetyldithio) compounds such as **14**, obtained from *gem*-disulfenyl dichlorides **11** (cf. Section 4.6) and thioacetic acid [27]:



14 **15** (59)

Instead, sulfur-rich heterocycles were formed by an obscure mechanism; cf. Sections 2.3 and 2.5

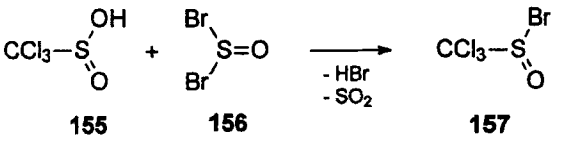
5. SULFINIC ACID DERIVATIVES

Base sensitive sulfinyl chlorides such as 2,2,2-trichloroethanesulfinyl chloride CCl_3CH_2SOCl can be oxidized with dimethyl sulfoxide to the corresponding sulfonyl chloride without loss of HCl [86]. Sodium adamantane-1-sulfinate reacts with thiophosgene in an unexpected fashion to yield tris(adamantan-1-ylsulfonyl)methane, $(1\text{-}C_{10}H_{15}SO_2)_3CH$ [103].

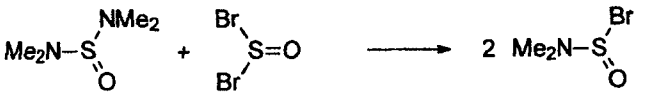
5.1. Sulfinyl Bromides

The apparently trivial task of preparing the first examples of sulfinyl bromides such as **157** and **159** could be solved in a straightforward manner by treatment of trichloromethanesulfinic acid **155** and of *N*,*N*,*N*′,*N*′-tetramethyl sulfurous diamide **158**, respectively, with purified commercial thionyl bromide **156** [104].

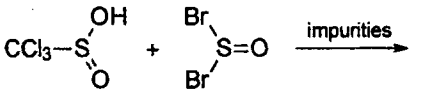
However, when trichloromethanesulfinic acid **155** was treated with technical grade thionyl bromide **156** the products, isolated in substantial amounts, were bromodichloromethanesulfenyl bromide **160** and 1,4,4,7-tetrabromo-1,1,7,7-tetrachloro-2,3,5,6-tetrathiaheptane **161**, see Scheme 18 [104]. The mechanism of this exotic reaction (where S(IV) starting materials lead to S(II) products) remains as obscure today as when it was first encountered. Formally, the tetrathiaheptane can be regarded as the product of thiophilic addition of 2 mol of bromodichloromethanesulfenyl bromide **160** to carbon disulfide, but there is no obvious reason for this reaction to take place.



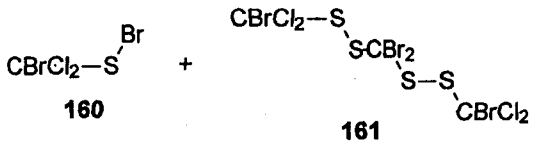
155 156 157 (60)



158 156 159 (61)



155 156

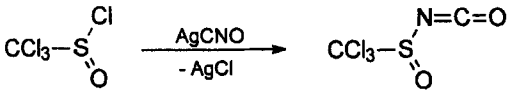


160 161 (62)

SCHEME 18

5.2. Trichloromethanesulfinyl Isocyanate

The unprecedented title compound **163** could be obtained in a simple manner from trichloromethanesulfinyl chloride **162** and silver cyanate:

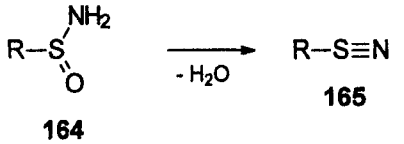


162 163 (63)

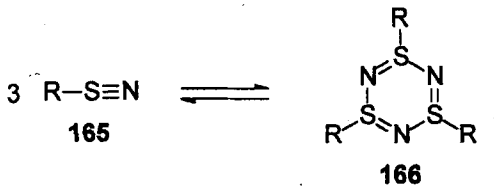
Because of similar boiling points the resulting mixture of sulfinyl isocyanate **163** and starting sulfinyl chloride **162** could not be separated, but was used as such for further derivatization. With ammonia *N*-(trichloromethanesulfinyl)urea,

$CCl_3SONHCONH_2$, was formed, and with ethanol *N*-(trichloromethanesulfinyl)-urethane, $CCl_3SONHCOOEt$ [105].

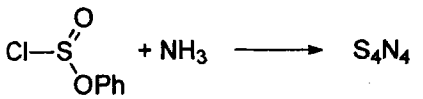
5.3. Thianitriles (Thiazyl Derivatives)



164 **165** (64)



165 **166** (65)



168 (66)

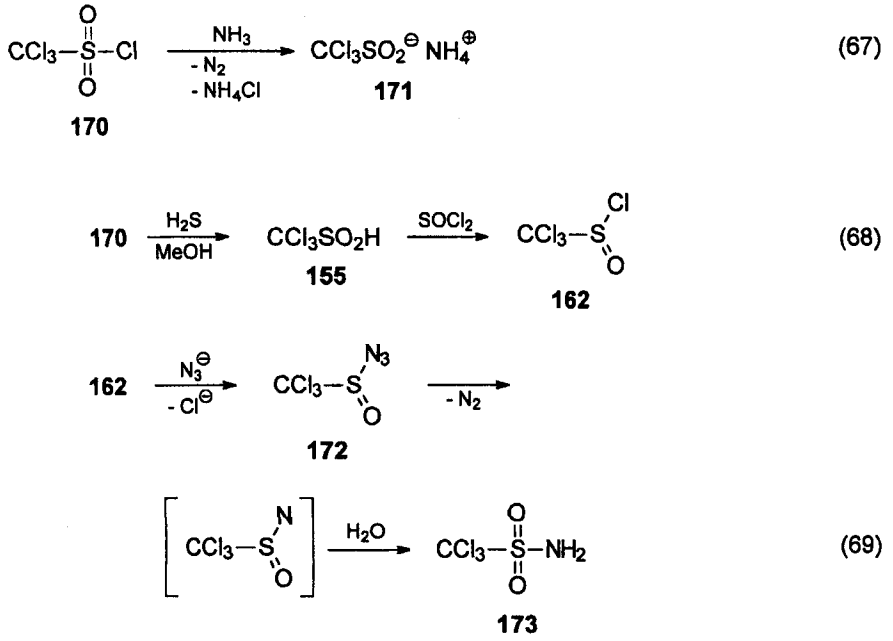
SCHEME 19

Early and, in retrospect, somewhat naive attempts to generate thianitriles (thiazyl derivatives) R–S≡N **165** (or, more likely, their trimers, the $1\lambda^4,3\lambda^4,5\lambda^4$-trithia-2,4,6-triazines **166**) by dehydration of sulfinamides R–SO–NH_2 **164** (see Scheme 19 and equations (64) and (65)) met with little success. A severe handicap was the notorious inaccessibility and/or instability of most *N*-unsubstituted sulfinamides **164**. Thus, treatment of the few available sulfinamides **164** with acetic anhydride only yielded their *N*-acetyl derivatives which could not be pyrolyzed to the desired thiazyl derivatives [46]. In the course of this work an attempt to prepare amidosulfurous acid phenyl ester H_2N–SO–OPh **167** from chlorosulfurous acid phenyl ester Cl–SO–OPh **168** and gaseous ammonia led instead, somewhat surprisingly, to the neat formation of N_4S_4, 2,4,6,8-tetraazy-1,3,5,7-tetrasulfy[$08.0^{1,5}.0^{3,7}$]tricycle (tetranitrogen tetrasulfide); cf. equation (66) [46].

Another, more sophisticated, but nonetheless fruitless effort began with the preparation of *N*-sulfinylphosphinimines R–SO–N=PPh_3 **169** (a then new class of compounds) from triphenylphosphinimine and sulfinyl chlorides. Unfortunately, their pyrolysis failed to yield the expected R–S≡N **165** and Ph_3PO. With, for instance, R = CCl_3 the only volatiles obtained from the pyrolysis of **169** were a mixture of bis(trichloromethyl)-oligosulfanes $CCl_3S_nCCl_3$ [106].

6. SULFONIC ACID DERIVATIVES

6.1. Sulfonamides

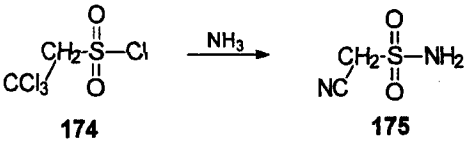


(67) (68) (69)

SCHEME 20

Contrary to popular belief the conversion of, say, trichloromethanesulfonyl chloride **170** to the corresponding sulfonamide **173** is not trivial. As shown in Scheme 20 the simple reaction between **170** and NH_3 leads to ammonium trichloromethanesulfinate **171** according to equation (67) because of the oxidizing properties of the positivized chlorine atom in **170**. This salt, with a virtually identical elemental composition, could easily be confused with the sulfonamide **173**. We were able to avail ourselves of a previously underutilized procedure, i.e. the reaction path involving trichloromethanesulfinyl azide **172**, available from **162** which in turn can be prepared from **170** (cf. equation (68)), to prepare the desired **173**; cf. equation (69) [107].

The preparation of 2,2,2-trichloroethanesulfonamide **175** from 2,2,2-trichloroethanesulfonyl chloride **174** and ammonia is likewise compromised, in this case by the concomitant conversion of the trichloromethyl group to a nitrile group:



(70)

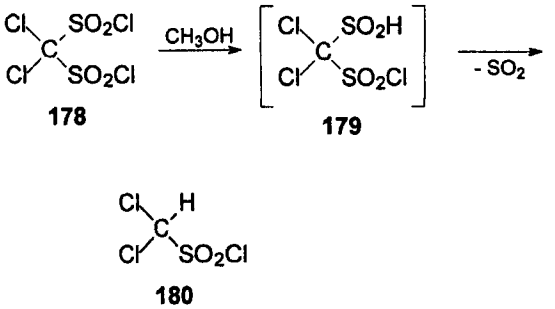
Also here, the sulfonamide could be obtained via the corresponding sulfinyl azide [107].

6.2. Fluoromethanesulfonyl Chloride

In our early work with potentially antileukemic busulfan analogs (cf. Sections 6.5 and 11.1.1), the virtual inaccessibility of fluoromethanesulfonyl chloride **176** had been a major obstacle. Thus, when the aqueous chlorination of 4-chlorobenzyl fluoromethyl sulfide **177** was shown by others to yield **176** and we could further improve and considerably simplify the synthesis of **177**, fluoromethanesulfonyl chloride **176** became available in overall 29% yield from commercially available (4-chlorophenyl)methanethiol [108].

6.3. Dichloromethanedisulfonyl Dichloride

On the basis of the fact that trichloromethanesulfonyl chloride **170** is readily reduced to trichloromethanesulfinic acid **155** by hydrogen sulfide (cf. equation (68)), we found it worthwhile to investigate the corresponding reduction of dichloromethanedisulfonyl dichloride **178**. To our surprise **178** was smoothly reduced on mere dissolution in methanol (the solvent routinely used for the H_2S reduction of **170**) to yield, after subsequent loss of sulfur dioxide, dichloromethanesulfonyl chloride **180**:



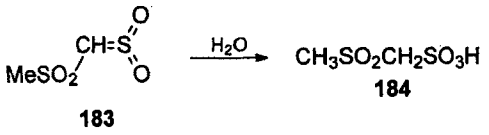
(71)

The same product was obtained when **178** was dissolved in acetic acid and reduced with hydrogen sulfide. Even *tert*-butylamine could serve as reducing agent with *N-tert*-butyldichloromethanesulfonamide $CHCl_2SO_2NH$-Bu-*t* as the final product [109].

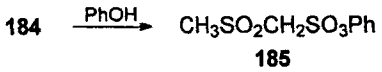
6.4. Methylsulfonylmethanesulfonic Acid and Bis(methylsulfonyl)methanesulfonic Acid

Our activities in the area of sulfonic acid alkylene esters, triggered by the interesting antileukemic properties of the classical drug busulfan **181a** and the experimental drug piposulfan **182a** (cf. Sections 6.5 and 11.1.1), required a varied portfolio of acceptor-substituted methanesulfonic acids. Among these were methylsulfonylmethanesulfonic acid, $MeSO_2CH_2SO_3H$, **184** and bis(methylsulfonyl)methanesulfonic acid, $(MeSO_2)_2CHSO_3H$, **187**, both of which were unknown at that time. As shown in Scheme 21 we were able to obtain both compounds from Opitz's methylsulfonylsulfene, $MeSO_2CH{=}SO_2$, **183** [110] as key intermediate [111]. The sulfonic acid **184** was formed by addition of water to **183** and isolated in the shape of its sodium and silver salt, respectively; cf. equation (72). Phenyl methylsulfonylmethanesulfonate, $MeSO_2CH_2SO_3Ph$, **185**, obtained from the sulfene **183** and phenol, could be methylsulfonylated with methanesulfonyl chloride. The resulting ester $(MeSO_2)_2CHSO_3Ph$ **186**

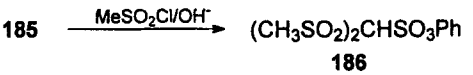
was then solvolyzed with methanol to yield the corresponding sulfonic acid, $(MeSO_2)_2CHSO_3H$, **187**; cf. equations (73)–(75).



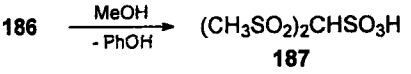
183 **184** (72)



184 **185** (73)



185 **186** (74)



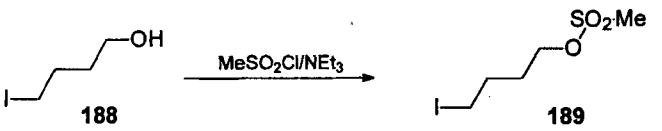
186 **187** (75)

SCHEME 21

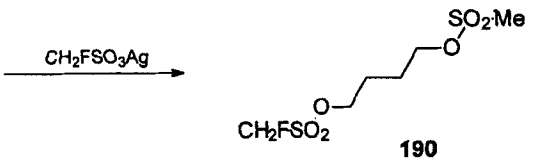
6.5. Sulfonic Acid Esters

For the purposes of our extensive antileukemic project aimed at an optimization of busulfan-type compounds (cf. Section 11.1.1), we had to prepare a total of 124 symmetrical bis(sulfonates) from the corresponding primary alkyl iodides $I–CH_2–X–CH_2–I$ and silver sulfonates, a well-established method for the preparation of sulfonic acid esters [6,112]. For the preparation of new sulfonic acids see Sections 6.2 and 6.4.

The only unsymmetrical compound in this series, i.e. **190**, was prepared according to [112]:



188 **189**

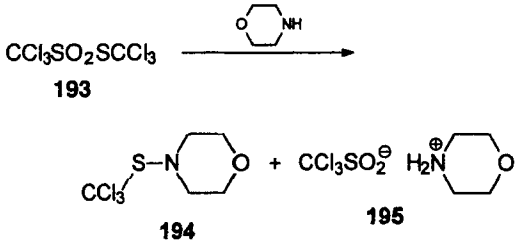


190 (76)

6.6. Thiosulfonic Acid Derivatives

S-Benzhydryl *p*-toluenethiosulfonic acid ester 4-$MeC_6H_4SO_2SCHPh_2$ **191** could be made from potassium *p*-toluenethiosulfonate and benzhydryl bromide while the standard reagent benzhydryl chloride failed to react under the same conditions [113]. *p*-Toluenethiosulfonic acid anhydrosulfide 4-$MeC_6H_4SO_2SSO_2C_6H_4Me$-4 **192** was found to react with with the anions *O*-ethyl dithiocarbonate, benzyl trithiocarbonate and *N,N*-dimethyldithiocarbamate to form the corresponding mixed disulfides [114].

S-(Trichloromethyl) trichloromethanethiosulfonate $CCl_3SO_2SCCl_3$ **193** and the analog $CCl_3SO_2SSCCl_3$ **194** could be prepared by standard procedures. Compound **193** reacts with morpholine according to [115]

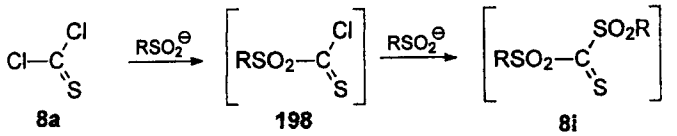


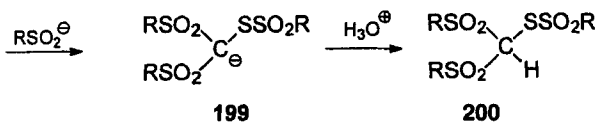
(77)

7. THIOCARBONYL COMPOUNDS

While α-thioxo sulfones appear to be much too reactive for conventional synthetic work we were pleased to be able to show that the presence of an additional α-substituent with at least one free electron pair is beneficial and thus *C*-sulfonylthioformamides $R^1SO_2CSNR^2R^3$ **196** (cf. Section 7.4) and *C*-sulfonyldithioformates $R^1SO_2CSSR^2$ **54** (cf. Section 7.5) could be readily prepared and exploited for mechanistic and preparative purposes.

The reaction between thiophosgene **8a** and sulfinate anions **197** is a case in point: the elusive *C*-sulfonylthioformyl chloride **198** and the disulfonylmethanethione **8i** can be neither observed nor trapped; the finally isolated product is formed by addition of **197** to **8i** [116,117]





(78)

When the free sulfinic acid is used instead of the sodium sulfinate the yield is improved, but the course of the reaction remains unaffected [118].

Our qualitative reinvestigation of the thiation of thiophosgene **8a** with S_8 at elevated temperature showed, beyond the previously observed 3,3,6,6-tetrachloro-1,2,4,5-tetrathiane **12a**, the presence of a plethora of $C_xCl_yS_z$ compounds including

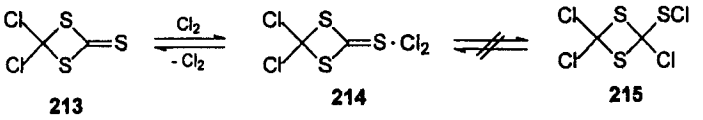
3,3,5,5-tetrachloro-1,2,4-trithiolane **13a**, 2,2,4,4,6,6-hexachloro-1,3,5-trithiane **201** and 4,4,7,7-tetrachloro-1,2,3,5,6-pentathiepane **202** [119].

7.1. Trithiocarbonic Acid Chemistry

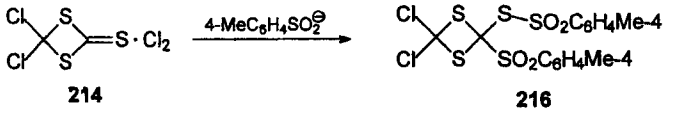
By treatment of metal trithiocarbonates with perhaloalkanesulfenyl chlorides RSCl or with trichloromethanethiosulfenyl chloride CCl_3SSCl **203** we could prepare the isolable pentathiodipercarbonates $(RSS)_2C{=}S$ **204** (concerning the oxidation of these compounds to the corresponding sulfines, cf. Section 8.3) and bis(trichloromethyltrithio)-methanethione $(CCl_3SSS)_2C{=}S$ **205**. On the other hand, attempts to synthesize bis(pentachlorophenyl)pentathiodipercarbonate $(C_6Cl_5SS)C{=}S$ **206** only led to bis-(pentachlorophenyl)trisulfane **207**, presumably by spontaneous loss of CS_2 from **206**. Compound **204** can further add chlorine, SCl_2 or sulfenyl chlorides RSCl to yield the sulfenyl chlorides $(RSS)_2CClSCl$ **208**, the thiosulfenyl chlorides $(RSS)_2CClSSCl$ **209** and the trisdisulfides $(RSS)_3CCl$ **210**, respectively. Thiosulfenyl chlorides RSSCl **30** add to **204** to yield the trisulfanes $(RSS)_2CClSSSR$ and to **205** to give the tristrisulfanes $(RSSS)_3CCl$ **211**.

The sulfenyl chlorides $(RSS)_2CClSCl$ **208** can rearrange to the trisulfanes $RSSCCl_2SSSR$ **212** [120,121].

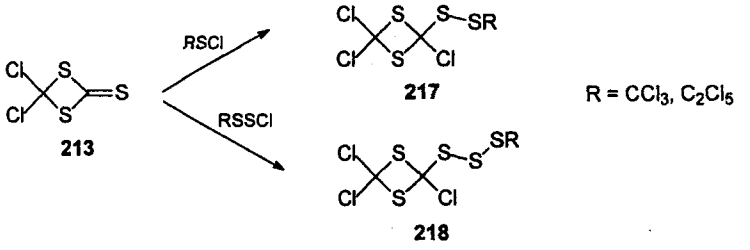
4,4-Dichloro-1,3-dithietane-2-thione (dichloromethylene trithiocarbonate) **213** was studied with respect to its addition of chlorine, sulfenyl chlorides and thiosulfenyl chlorides; see Scheme 22. Interestingly, the π-complex **214** reacts with *p*-toluenesulfinate anions **197** to yield the same product **216** which one would have expected from the isomeric α-chloro sulfenyl chloride **215** [122].



213 **214** **215** (79)



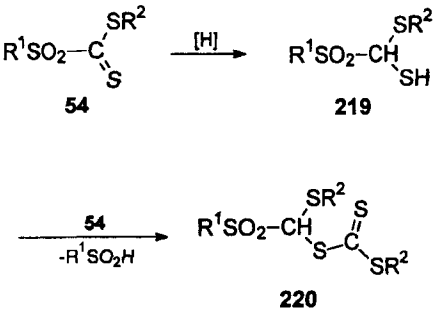
214 **216** (80)



213 **217** **218** R = CCl_3, C_2Cl_5

SCHEME 22

The reduction of *C*-sulfonyldithioformates **54** with a variety of reagents leads to the corresponding trithiocarbonates **220** as a consequence of the thioacylating properties of **54** *vis-à-vis* the primary reduction product **219** [54,123]:



(81)

7.2. Thiocarbamoyl Chlorides

The until then elusive alkylenebis(thiocarbamoyl chlorides) **221** could be obtained neatly and efficiently by treatment of the corresponding *N,N'*-bis(trimethylsilyl)-alkane-α,ω-diamines **222** with thiophosgene **8a** [124]. For reactions of thiocarbamoyl chlorides **223** leading to *C*-sulfonylthioformamides **196**, see Section 7.4.

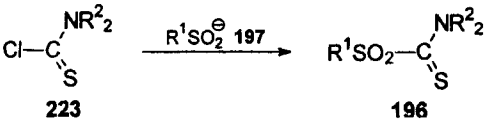
7.3. Chlorodithioformates

A review of ours summarizes early work with chlorodithioformates ClCSSR **7** [125]. In one of our most recent papers we could show that, at elevated temperatures, chlorodithioformates **7** do react with simple alka-1,3-dienes to give the corresponding Diels–Alder adducts [126]. For reactions of chlorodithioformates **7** leading to *C*-sulfonyldithioformates **54**, see Section 7.5.

The 1,3-dipolar cycloaddition reaction of ethyl chlorodithioformate **7a** with diazomethane leads, with spontaneous loss of HCl, to a 68:32 mixture of 2-ethylthio-1,3,4-thiadiazole and 5-ethylthio-1,2,3-thiadiazole [127].

7.4. *C*-Sulfonylthioformamides

N,N-Dialkylthiocarbamoyl chlorides **223** neatly *S*-thioacylate sulfinate anions **197** to yield *C*-sulfonylthioformamides **196** [128,129]:

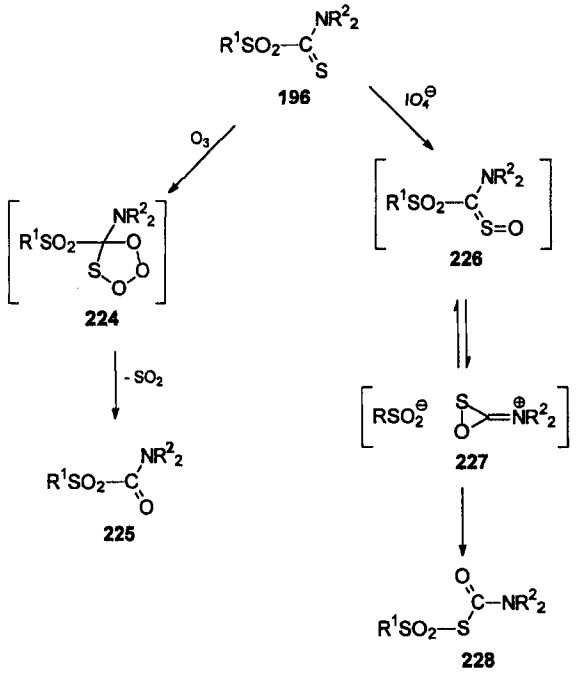


(82)

C-Sulfonylthioformamides **196** readily thioacylate cyanide anions as well as carbanions to give the corresponding thioamides [130].

The oxidation of *C*-sulfonylthioformamides **196** can take two different courses: ozone cycloadds to the thiocarbonyl group as a 1,3-dipole and the resulting adduct **224** suffers fragmentation to the *C*-sulfonylformamide **225** and, presumably, SO_2; oxidation of **196** with, for example, periodate gives the corresponding *S*-oxide **226** which

subsequently rearranges to **228** without loss of sulfur; see Scheme 23. The driving force for this rearrangement comes undoubtedly from the favorable soft–soft HSAB interactions en route to the incipient S–S bond of the ion pair **227** [129,131].

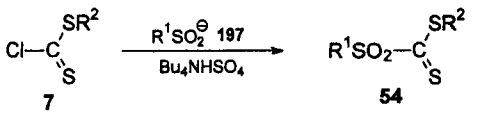


SCHEME 23

N,N-Dimethyl-*C*-(*p*-tolylsulfonyl)thioformamide **196a** reacts with diazomethane to form, as the result of a 1,3-dipolar cycloaddition, followed by spontaneous loss of sulfinic acid, a 94:6 mixture of 5-(dimethylamino)-1,2,3-thiadiazole and 2-(dimethylamino)-1,3,4-thiadiazole [127].

7.5. *C*-Sulfonyldithioformates

C-Sulfonyldithioformates **54** are readily obtained from chlorodithioformates ClCSSR **7** and sulfinate anions **197** in the presence of a phase transfer reagent [54,132,133]:



(83)

C-Sulfonyldithioformates **54** react with carbanions in a number of ways, initiated by carbophilic and/or thiophilic attack of the carbanion on the thiocarbonyl group of **54** [134,135].

The thiocarbonyl group of *C*-sulfonyldithioformates **54** readily participates in hetero-Diels–Alder reactions with simple alka-1,3-dienes and with cyclopenta-1,3-diene [134,136]. *C*-Sulfonyldithioformates **54** react with anthracene and 9-methylanthracene in a hetero-Diels–Alder fashion. The hetero-Diels–Alder adducts readily eliminate sulfinic acid to form the corresponding anthracene-9-dithiocarboxylic acid esters [137].

Thermal ene reactions between *C*-sulfonyldithioformates **54** and tetramethylallene (2,4-dimethylpenta-2,3-diene) are especially facile [134]. In addition to these thermal ones photochemical ene reactions of **54** have also been observed. Thus, for instance, pentachlorophenyl *p*-tolylsulfonyldithioformate **54a** and (1*S*)-(−)-β-pinene react photochemically to give a mixture of the diastereoisomers (1*R*)-(+)- and (1*S*)-(−)-[(1*S*)-(2-pinen-10-yl)thio-*p*-tolylsulfonyl-pentachlorophenylthio]methane [138].

Photochemical [2+2] cycloadditions of **54** to alkenes have been observed. The cycloadducts subsequently rearrange to β-sulfonyl dithiocarboxylates **229** [139].

The 1,3-dipolar addition of diazoalkanes to **54** leads, with loss of nitrogen, to the corresponding thiiranes [127].

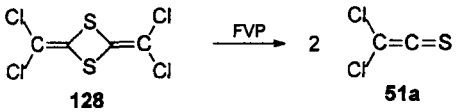
Compounds **54** react with S_4N_4 to give the corresponding *N*,*N*′-bisalkylidenesulfur diamides $R^1SO_2(R^2S)C{=}N{-}S{-}N{=}C(SR^2)SO_2R^1$ **230** [140].

7.6. Thioketenes

This work benefited greatly from congenial cooperation with Ernst Schaumann (Technical University of Clausthal, Germany). A concise compilation of thioketene chemistry is provided in Ref. [141].

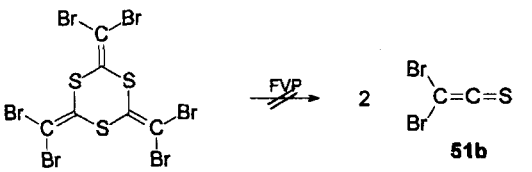
7.6.1. Dichlorothioketene

While a considerable number of, mostly highly reactive, thioketenes had been fully characterized no clear-cut trapping experiments with 2,2-dichloroethene-1-thione (dichlorothioketene) **51a** had been reported. When its formal dimer, 2,4-bis(dichloromethylene)-1,3-dithietane **128** became available in my laboratory by non-thioketene chemistry (cf. Section 4.2.3), its flash vacuum pyrolysis offered itself as an obvious project. This pyrolysis was carried out in the laboratory of Ernst Schaumann (Technical University Clausthal, Germany) and did indeed generate dichlorothioketene **51a** which could be trapped by hetero-Diels–Alder reaction with cyclopenta-1,3-diene; see Scheme 24, equations (84) and (85) [142].



128 51a (84)

231 (85)



233 51b (86)

SCHEME 24

Interestingly, the likewise known trimer of dichlorothioketene, 2,4,6-tris(dichloromethylene)-1,3,5-trithiane **232**, cannot be pyrolyzed to dichlorothioketene **51a**. The same is true of the analogous 2,4,6-tris(dibromomethylene)-1,3,5-trithiane **233** which fails to give dibromothioketene **51b** on pyrolysis; cf. equation (86) [143].

Concerning thioketene work involving CS, cf. Subsection 3.5.

7.6.2. Thioalkyne-Derived Thioketenes

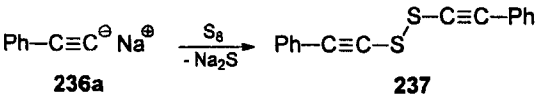
During work aimed at the synthesis of alk-1-yn-1-yl disulfides **234** [144] and of alk-1-yne-1-sulfenyl chlorides **235** [145] we discovered their spontaneous rearrangement to the corresponding thioketenes **51**; see Scheme 25.

(87)

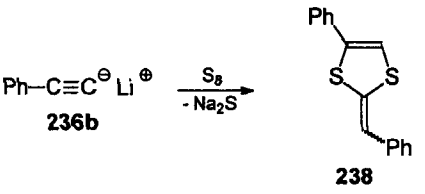
(88)

SCHEME 25

7.6.2.1. Alk-1-yn-1-yl Disulfide Derived Thioketenes When we surveyed the prior work concerning alk-1-yn-1-yl disulfides **234** we noted a report [146] describing the synthesis of bis(2-phenylethyn-1-yl) disulfide Ph–C≡C–S–S–C≡C–Ph **237** (only characterized by a melting point and an elemental analysis) by oxidation of sodium 2-phenylethyn-1-ide **236a** with sulfur; see Scheme 26, equation (89). When we tried to duplicate this reaction starting with the more readily prepared lithium 2-phenylethyn-1-ide **236b** we obtained instead the (*E*)- and (*Z*)-isomers of the dithiafulvene **238**, most likely formed by unsymmetrical dimerization of 2-phenylethene-1-thione (phenyl-thioketene) **51c** and/or its anion; cf. equation (90).

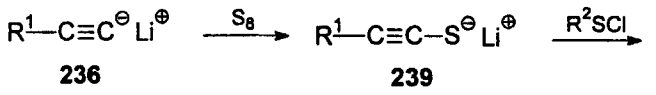


(89)

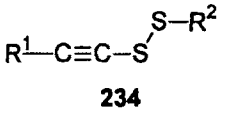


(90)

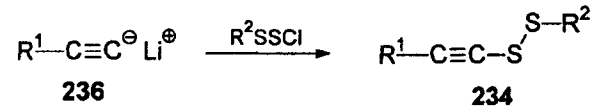
SCHEME 26



236 **239**



234 (91)

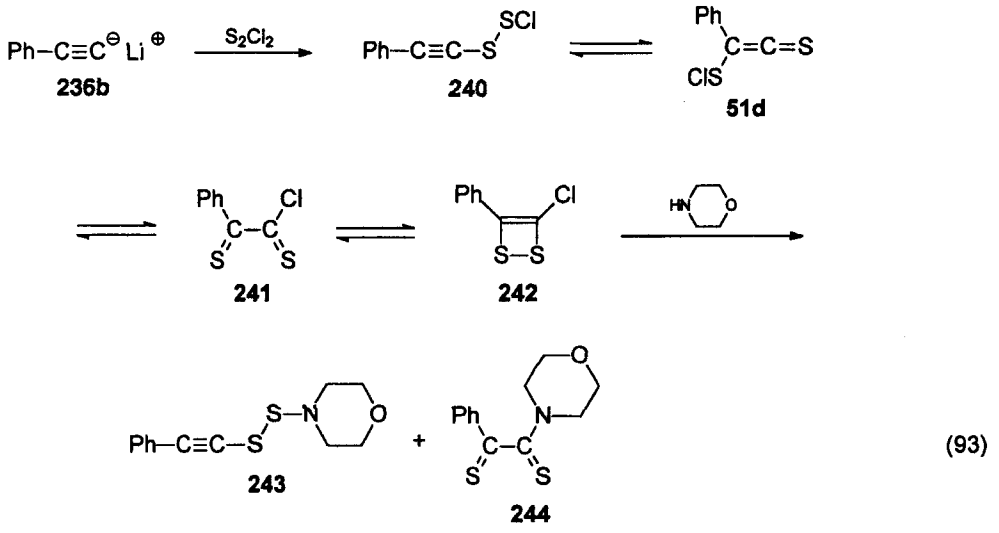


236 **234** (92)

SCHEME 27

We then developed two independent methods for the preparation of **234**; see Scheme 27. In this way we were able to obtain and characterize twelve authentic alk-1-yn-1-yl disulfides **234**. Six of them, for instance *t*-Bu–C≡C–S–S–CPh_3, possess unlimited shelf life, and five, for instance *t*-Bu–C≡C–S–S–Bu-*t*, suffer a spontaneous 1-thiapropargyl–3-thiaallenyl rearrangement to the corresponding thioketenes **51** according to equation (87).

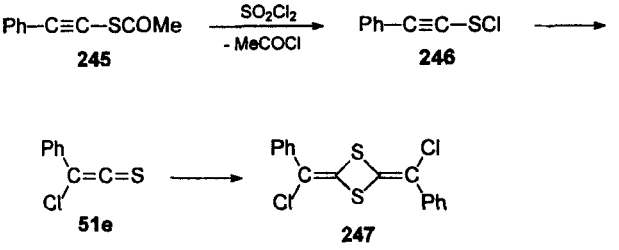
The unspecified mixture of tautomers formed by treatment of lithium 2-phenylethyn-1-ide **236b** with S_2Cl_2 on quenching with morpholine yields 4-morpholino 2-phenylethyn-1-yl disulfide **243** and 2-phenyl-2-thioxoethanethio-4-morpholide **244** [144]:



236b **240** **51d** **241** **242** **243** **244** (93)

7.6.2.2. Alk-1-yne-1-sulfenyl Chloride Derived Thioketenes When we generated 2-phenylethyne-1-sulfenyl chloride **246** from *S*-(2-phenylethyn-1-yl) thioacetate **245** and SO_2Cl_2 we observed a spontaneous rearrangement to the corresponding thioketene

51e which immediately dimerized to the corresponding (*E*)-isomeric 1,3-dithietane **247** [145]:



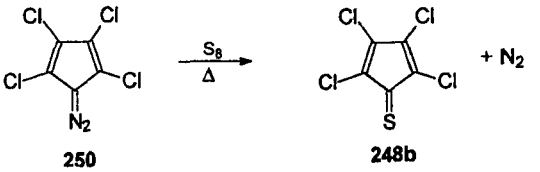
(94)

7.7. Thiopeptides

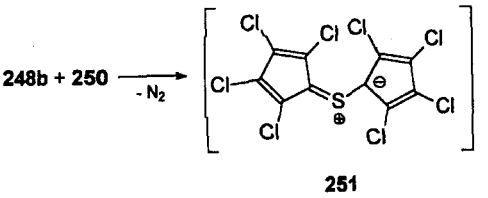
A number of graduate students with synthetic thiopeptide projects centered on 5-thioxo-L-proline (for which an improved synthetic procedure was developed) [147] were 'inherited' on my Århus colleague Sven-Olov Lawesson's untimely death in 1985. These projects were by and large completed along the lines laid down upon their conception in the Lawesson group [147–151]. For instance, in one of the projects 5-thioxo-L-proline was used as the *N*-terminal of a series of melanocyte stimulating hormone-inhibiting factor analogs [151]. A good deal of this work profited from fruitful collaboration with Claudio Toniolo (University of Padua, Italy) and his group. For other biologically relevant thioamide work, see Sections 11.1.3 and 11.1.4.

7.8. Cyclopenta-2,4-diene-1-thiones

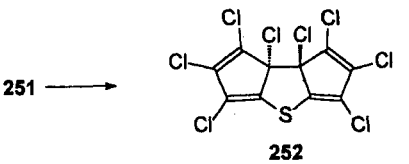
Our quest for the elusive cyclopenta-2,4-diene-1-thiones **248** did not lead to isolable thioketones but to a cornucopia of exciting cycloadditions and rearrangements including the discovery of a transient *N*-thionitrosoimine **249**.



(95)



(96)

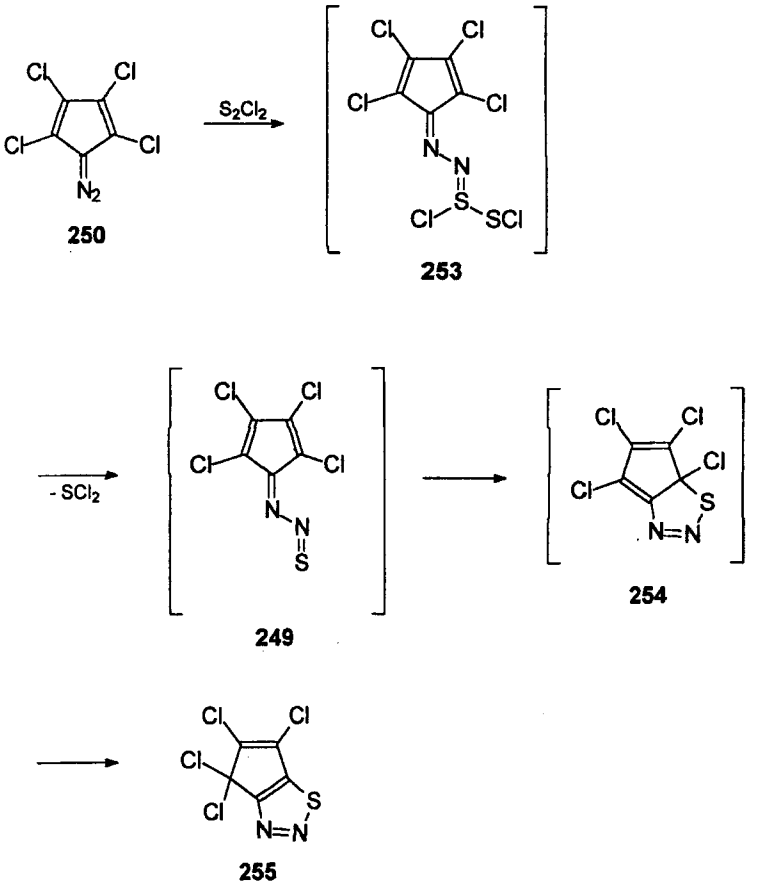


(97)

SCHEME 28

On the basis of the known fact that the parent cyclopenta-2,4-diene-1-thione **248a** is too unstable for classical synthetic work we explored, in cooperation with Kurt V. Mikkelsen (now at the University of Copenhagen, Denmark) who provided the quantum chemical expertise, both the theoretical and the experimental possibility of stabilizing this system by electronic and/or steric effects of substituents [152].

Our first attempt was devoted to perchlorination, i.e. we prepared the known 1-diazo-2,3,4,5-tetrachlorocyclopenta-2,4-diene **250** and let it react with molten S_8. Apparently, 2,3,4,5-tetrachlorocyclopenta-2,4-diene-1-thione **248b** is indeed generated, but trapped by **250** to form, after loss of nitrogen, the thiocarbonyl *S*-ylide **251** which cyclizes to the chiral *trans*-substituted hydrothiophene derivative **252**; see Scheme 28 [153]. It is remarkable that **252** fails to form an aromatic thiophene system which would be possible by double chlorine migration. When we treated **250** (or the corresponding hydrazone) with S_2Cl_2 or SCl_2 the expected loss of nitrogen did not take place. Instead, an *N*-thionitrosoimine **249** was formed which cyclized with concomitant chlorine migration to give the aromatic 4,4,5,6-tetrachloro-4*H*-cyclopenta-1,2,3-thiadiazole **255** [154]:

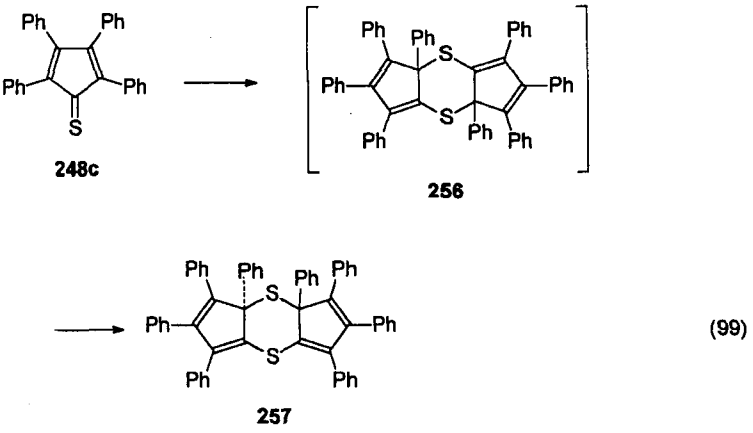


250 **253** **249** **254** **255**

(98)

2,3,4,5-Tetraphenylcyclopenta-2,4-diene-1-thione **248c** is apparently formed both in the thionation of the corresponding ketone and by sulfuration of the corresponding

diazo compound, but immediately forms *trans*-(±)-1,2,3,3a,4a,5,6,7-octaphenyl-3a*H*,4a*H*-dicyclopenta[*b*,*e*][1,4]dithiin **257** by head-to-tail [3+3] dimerization of **248c** to **256**, followed by phenyl migration [152]:



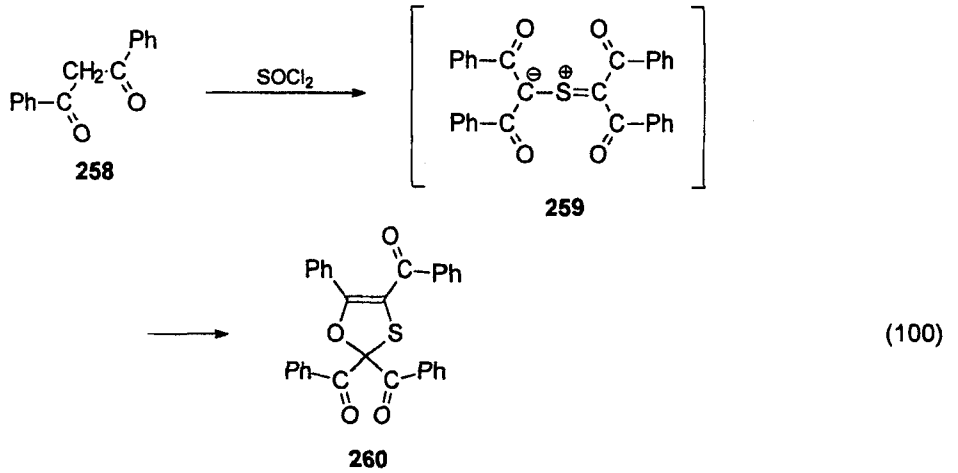
(99)

Thionation of 2,3-diphenylinden-1-one under Lawesson conditions (LR, boiling toluene) only leads to the known 2,2′,3,3′-tetraphenylbiindenylidene (of as yet undetermined stereochemistry), probably via formation of 2,3-diphenylindene-1-thione, [2+2] dimerization of the thione and subsequent sulfur extrusion from this dimer [46].

8. MISCELLANEOUS SULFUR CUMULENES

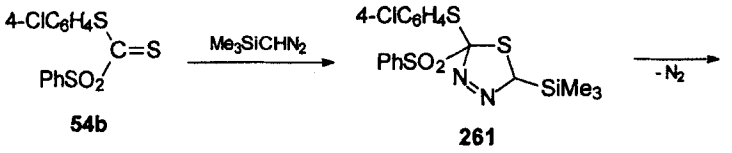
8.1. Thiocarbonyl *S*-Ylides

An attempt to prepare 2-chloro-1,3-dioxo-1,3-diphenylpropane-2-sulfenyl chloride **26e** from 1,3-diphenylpropane-1,3-dione (dibenzoylmethane) **258** and $SOCl_2$ led instead to 2,2,4-tribenzoyl-5-phenyl-1,3-oxathiole **260**, most likely formed by cyclization of the corresponding thiocarbonyl *S*-ylide **259** [155]:

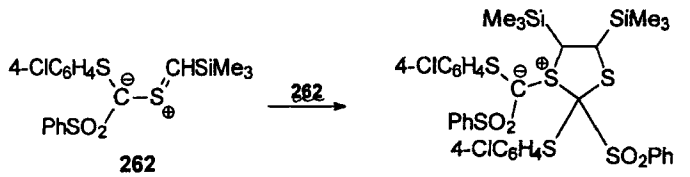


(100)

An unprecedented unsymmetrical dimerization of a transient thioaldehyde *S*-ylide **262** could be observed when we treated the *C*-sulfonyldithioformate **54b** (cf. Section 7.5) with diazo(trimethylsilyl)methane:



54b **261**



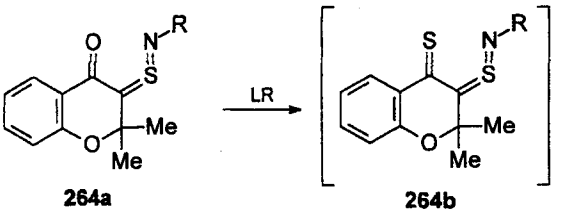
262 **263** (101)

In this cycloaddition one molecule of **262** plays the role of a 1,3-dipole and another molecule of **262** serves as dipolarophile [156].

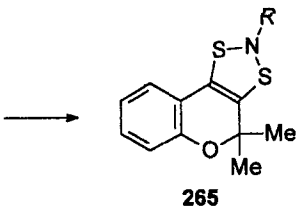
8.2. Thiocarbonyl *S*-Imides

The *C*-sulfonyldithioformates **54** (cf. Section 7.5) readily add chlorine to form the corresponding α-chloroalkanesulfenyl chlorides **26** which in turn react with primary amines to give characteristically orange-colored thiocarbonyl *S*-imides **264** which are isolable when the *N*-substituent is particularly bulky such as *tert*-butyl or adamantan-1-yl [54,55,135,157–159].

The transient dithione *S*-imide **264b**, obtained from the corresponding α-oxo thione *S*-imide **264a**, suffers electrocyclization to the isomeric 1,3,2-dithiazole **265**, the first unsymmetrically substituted 1,3,2-dithiazole:



264a **264b**



265 (102)

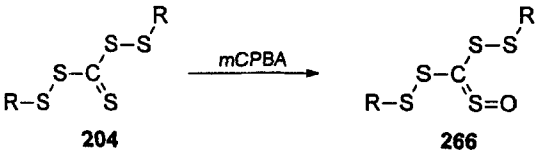
R = adamantan-1-yl

In a concomitant reaction the Lawesson monomer acts as dipolarophile *vis-à-vis* **264a** to form the novel 1,4,2,3-dithiazaphosphole ring system [160].

The pyrolysis of some thione *S*-imides **264** gave in an obscure reaction, probably involving the corresponding thiosulfines **5** (cf. Section 2.1.2), the corresponding 1,2,4-trithiolanes [158,159].

8.3. Sulfines

Bis(trichloromethyl) pentathiodipercarbonate and bis(pentachloroethyl) pentathiodipercarbonate $(RSS)_2C{=}S$ ($R = CCl_3$, C_2Cl_5) **204** (cf. Section 7.1) could be oxidized with 3-chloroperbenzoic acid to the stable corresponding sulfines $(RSS)_2C{=}S{=}O$ ($R = CCl_3$, C_2Cl_5) **266** [111,120]:



204 **266**

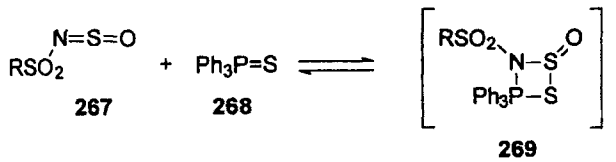
$R = CCl_3, C_2Cl_5$ (103)

8.4. Thiosulfines

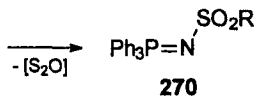
Our extensive work on thiosulfines **5** (and on the tautomeric dithiiranes **6**) is presented in Sections 2.1 and 7.

8.5. *N*-Sulfinyl Compounds

In our work with *N*-sulfinylamines and -sulfonamides we explored the quasi-Wittig reaction (an example is shown in equation (104)) as a means for the conversion of, *inter alia*, compounds with sulfur- or phosphorus-centered double bonds to the corresponding imines; cf. also Section 8.7 [119,128,161–165].



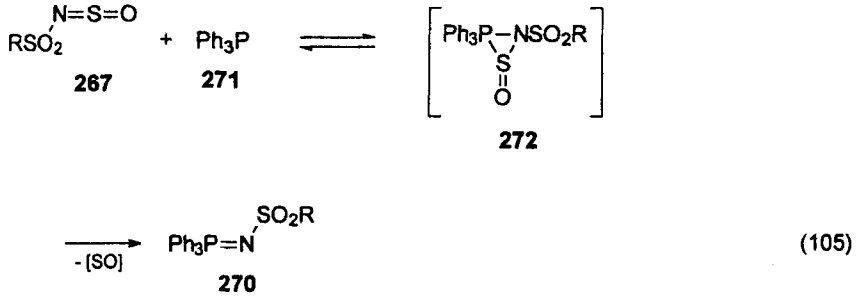
267 **268** **269**



270 (104)

Pentachloroethanesulfenamide **119** [90] (cf. Section 4.2.2) and thiophenesulfenamides [166] (cf. Section 9.1) can be readily derivatized to the corresponding *N*-sulfinylsulfenamides R–S–N=S=O.

N-Sulfinylsulfonamides **267** react with triphenylphosphine **271** according to



(105)

Analogous reactions take place with with triphenylarsine and triphenylstibine [162].

8.6. *N*-Thiosulfinyl Compounds

The remarkably stable *N*-(thiosulfinyl)pentachloroethanesulfenamide C_2Cl_5–S–N=S=S **122** could be obtained from pentachloroethanesulfenamide C_2Cl_5–S–NH_2 **119** and S_2Cl_2; cf. Section 4.2.2 [90].

8.7. Sulfur Diimides

According to a chance observation aromatic sulfinamides $ArSONH_2$ **273** react with trichloromethanesulfenyl chloride **2** to form (in very low yield) *N*-arylsulfenyl-*N'*-arylsulfonylsulfur diimides ArSN=S=NSO_2Ar **274** [167]. A more rational approach to the latter compounds is the treatment of arenesulfonamides with *N,N'*-disulfonylsulfur diimides RSO_2N=S=NSO_2R **275**. Compounds **274** on treatment with primary or secondary aliphatic amines disproportionate to yield, *inter alia*, *N,N'*-disulfenylsulfur diimides ArSN=S=NSAr **276** [168].

8.8. Carbon Disulfide

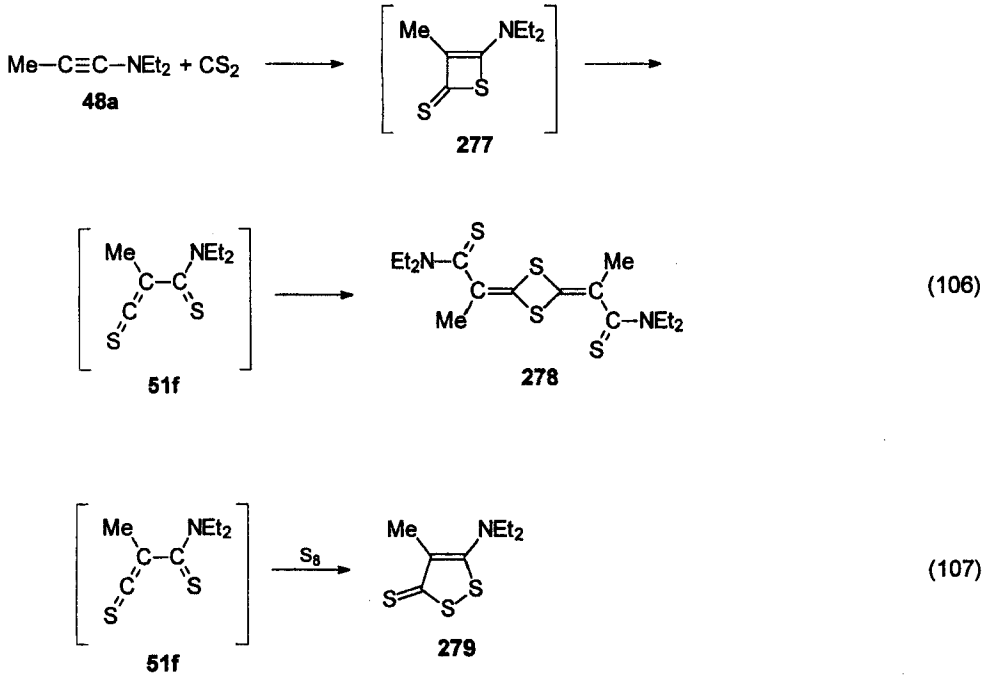
8.8.1. The Electrochemical Reduction of Carbon Disulfide

Early studies by others of the electrochemical reduction of CS_2 had invoked the intermediacy of CS in a number of secondary reactions. Since several of these postulates ran contrary to our own experience with the chemistry of CS (cf. Section 3), we investigated this reduction in depth. We could rule out any involvement of CS. A permethylated secondary product of the electrochemical reduction of CS_2 could be shown to possess the 4,5-bis(methylthio)-2-[bis(methylthio)methylene]-1,3-dithiole rather than the previously postulated 2,3,5,6-tetrakis(methylthio)-1,4-dithiin structure [38].

8.8.2. The Reaction of Carbon Disulfide with N,N-Diethylprop-1-yn-1-amine

N,N-Diethylprop-1-yn-1-amine **48a** reacts readily and in different ways with CS_2, S_8 and CS_2–S_8. Since spectroscopy could not produce unambiguous structure proofs our stable key products were characterized by single-crystal X-ray crystallography.

The primary [2+2] cycloaddition between **48a** and CS_2 leads to a highly strained four-membered ring system **277** which apparently ring opens to the α-thioxo thioketene **51f** which in turn dimerizes to the desaurin **278**; see Scheme 29, equation (106).



SCHEME 29

In the presence of S_8 the α-thioxo thioketene **51f** is immediately sulfurated to the corresponding 1,2-dithiole-3-thione **279**; cf. equation (107).

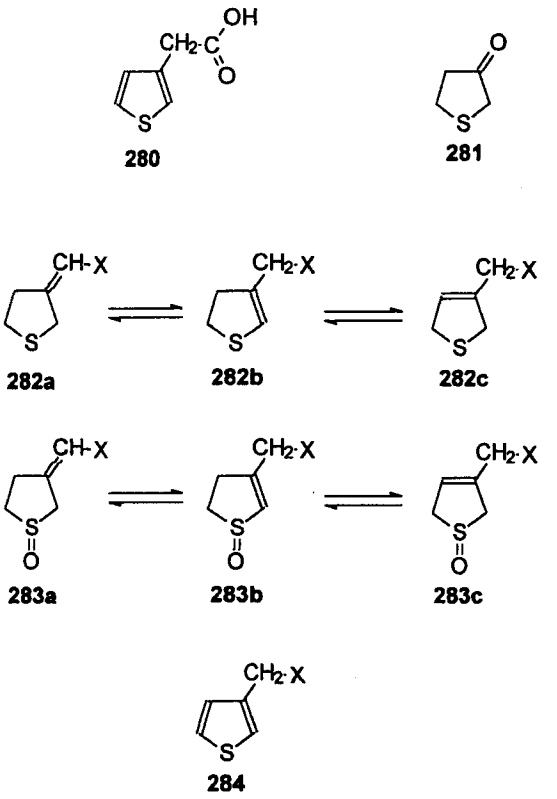
The reaction of **48a** with S_8 leads to a multitude of products which remained unidentified in our investigation [169].

9. HETEROCYCLIC SULFUR CHEMISTRY

9.1. Thiophenes

Thiophene-3-acetic acid **280** is an important intermediate in drug synthesis, but, as my friends in the drug industry told me, no really elegant synthesis of **280** had evolved yet. We decided to try our luck by focusing on the readily available tetrahydrothiophen-3-one **281** as a possible precursor of **280**. By a standard Knoevenagel procedure **281** was converted to the corresponding nitrile and ester tautomer mixtures **282** which could be subsequently oxidized to the corresponding sulfoxides **283**; see Scheme 30 [170]. Unfortunately, all efforts to dehydrate these sulfoxides to the corresponding thiophene

derivatives **284** failed [46].



SCHEME 30

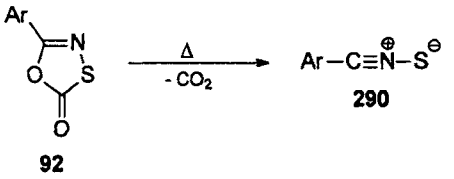
2,2′-Dithienyl disulfide **285** had been described in the literature but without satisfactory NMR data. We carried out a painstaking analysis of the ^{1}H- and the ^{13}C-NMR spectrum of **285**, including APT and COSY correlations [171].

On the basis of the known acaricidal properties of a variety of chloroaryl sulfides such as the commercial 4-chlorophenyl-2,4,5-trichlorophenyl sulfide 4-$C_6H_4ClSCH_2Cl_3$-2,4,5 **286** known under the trade names Tetrasul, Animert and V 101, we tried to prepare a series of chlorothienyl sulfides and oligosulfides in the hope of similar biological activity combined with improved biological degradability. Since the biological test results were by and large disappointing only the pure chemistry involved in this project has withstood the test of time. As potential key intermediates in this work we prepared the new 5-chlorothiophene-2-sulfenyl chloride **287** [172], 3,4,5-trichlorothiophene-2-sulfenyl chloride **288** [166] and 3,4-dichlorothiophene-2,5-disulfenyl dichloride **289** (too unstable to be isolated, but derivatizable in solution) [166], in all cases by chlorination of the corresponding thiols which in turn were obtained from the corresponding lithium derivatives and S_8. These sulfenyl chlorides could be converted to a considerable

number of derivatives. However, reactions between **287** and thiols only yielded mixtures of the symmetrical disulfides rather than the unsymmetrical disulfides [172].

9.2. 1,3,4-Oxathiazol-2-ones

When we first came across the 1,3,4-oxathiazol-2-ones **92** (cf. Section 4.1.3), they immediately appeared interesting for two reasons. Their pyrolytic behavior (formation of nitrile, CO_2 and sulfur) suggested that the primary pyrolytic product (apart from CO_2) might be the corresponding nitrile *N*-sulfide **290**:



92 **290** (108)

Unfortunately, our early attempts to trap **290** in appropriate 1,3-dipolar addition reactions failed miserably [46]. Later, this very chemistry was pursued in other laboratories with great success. The second point of interest was the fact that **92** were labile towards base (with formation of the corresponding amide **91**) but remarkably stable towards strong acids and oxidants such as fuming nitric acid. Thus we undertook a study of the electrophilic aromatic substitution of 5-aryl-1,3,4-oxathiazol-2-ones **92** in order to characterize the 2-oxo-1,3,4-oxathiazol-5-yl group as a substituent in aromatic systems.

While NMR studies of 5-phenyl-1,3,4-oxathiazol-2-one **92a** unequivocally demonstrated acceptor properties of the 2-oxo-1,3,4-oxathiazol-5-yl group, similar to those of the methoxycarbonyl and the nitroso group, the nitration of **92a** with fuming nitric acid at −15 °C led to 28% *o*-, ≤18% *m*- and ≥54% *p*-substitution, i.e. not exactly the pattern expected of a deactivating, *m*-directing substituent [173]. In painstaking mechanistic investigations it was shown that the 2-oxo-1,3,4-oxathiazol-5-yl group is basically a −I,−M substituent, but changes to the −I,+M type when stabilizing the σ-complex involved in aromatic nitration. This is most strikingly seen in the nitration of 5-[4-(chloromethyl)phenyl]-1,3,4-oxathiazol-2-one **92b** with 55% substitution *ortho* to the chloromethyl group and 45% substitution *ortho* to the 2-oxo-1,3,4-oxathiazol-5-yl group, i.e. the two groups resemble each other strongly in their deactivating, *o,p*-directing properties [174].

10. MISCELLANEOUS SULFUR CHEMISTRY

10.1. Physical Organic Chemistry

Apart from the work described in Sections 10.1.1, 10.1.2 and 10.1.3, other of our investigations could also be classified as physical organic chemistry, for instance some of the work presented in Section 9.2.

10.1.1. The Acidity of Amides and Hydrazides

In the course of our work with the sulfenylation of simple amides and hydrazides (cf. Section 4.1.3), we found it necessary to determine the acidities of some key amides and hydrazides where appropriate literature data were lacking [175].

10.1.2. Hindered Rotation Around Formal Single Bonds

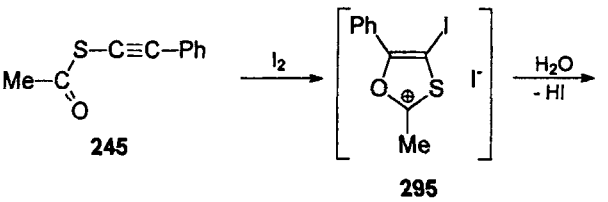
In work carried out in collaboration with Hans Jørgen Jakobsen (Aarhus University, Denmark) we determined, by NMR measurements, the barriers to internal rotations around formal single bonds in a collection of sulfen-, sulfin- and sulfonamides [176,177] as well as in 5-(dimethylamino)-1,3,4-oxathiazole 3,3-dioxide **291** [178].

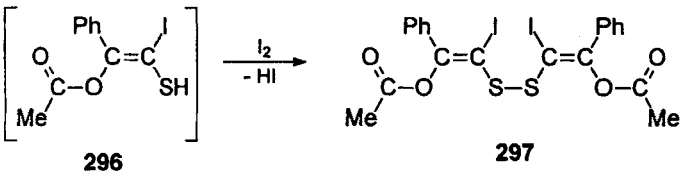
10.1.3. Structure Determination by Isotopic Labeling

The structure of tetrahydro-2-imino-1,3-thiazole-3-carboxamide **292** could not be rigorously excluded for a compound formed from 2-amino-4,5-dihydro-1,3-thiazole **293** and potassium cyanate and otherwise assumed to be 4,5-dihydro-2-ureido-1,3-thiazole **294.** A decision in favor of **294** could be arrived at by the use of ^{15}N-labeled potassium cyanate and subsequent Raney nickel desulfurization of the product to ^{15}N-labeled urea [179].

10.2. (*E*,*E*)-Bis(2-acetoxy-1-iodo-2-phenylethenyl) Disulfide

While we expected iodine to cleave the acyl–sulfur bond of *S*-(2-phenylethynyl) thioacetate **245** the actual attack took place at the C≡C triple bond and led, after several uncharted reaction steps, to (*E*,*E*)-bis(2-acetoxy-1-iodo-2-phenylethenyl) disulfide **297** [180]:



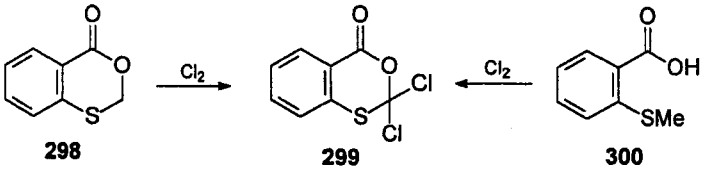


(109)

The structure of **297** was confirmed by single-crystal X-ray crystallography [181].

10.3. Thiosalicylic Acid Chemistry

In early work we investigated reactions of thiosalicylic acid with aldehydes giving the corresponding dithioacetals $RCH(SC_6H_4COOH\text{-}2)_2$ and/or 2-R-4*H*-3,1-benzoxathiin-4-ones [184–186]. Interestingly, the distillable 2,2-dichloro-4*H*-3,1-benzoxathiin-4-one **299** could be obtained by chlorination of both 4*H*-3,1-benzoxathiin-4-one **298** (obtained from thiosalicylic acid and formaldehyde) and 2-(methylthio)benzoic acid **300**; see Scheme 31 [4,3].



298 **299** **300**

SCHEME 31

10.4. Sulfur-Containing Pyridine Derivatives

Treatment of 2-pyridone with SCl_2 leads to bis(2-oxopyridin-5-yl) sulfide while 3-hydroxypyridine and 4-pyridone fail to give well-defined sulfur-containing products [187].

11. APPLIED CHEMISTRY

Many of the compounds prepared by us showed theoretical or practical potential as pesticides or drugs, but only the projects described in Sections 11.1 and 11.2 were intended as more or less ambitious exercises in *bona fide* medicinal and pesticide chemistry, respectively.

11.1. Medicinal Chemistry

11.1.1. Antileukemic Compounds

The bulk of our work in this area was devoted to a further elaboration of the bioalkylating lead compounds busulfan, $MeSO_3CH_2CH_2CH_2CH_2O_3SMe$, **181a** [188] and piposulfan, $MeSO_3CH_2CH_2CON(CH_2CH_2)_2NCOCH_2CH_2O_3SMe$, **182a** [189]. The former, a remarkably archaic compound in terms of state-of-the-art drug development, plays a small but important role in cancer chemotherapy and immunosuppression while the latter never developed beyond the experimental stage [190].

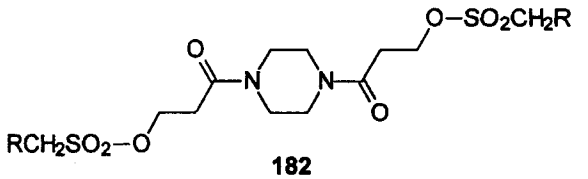
In a relatively ambitious and extensive project which to a large extent was carried out in close cooperation with the Bayer Company we undertook a study of busulfan and piposulfan analogs with a by-and-large retained alkylene center piece (which we felt had already been well documented as the optimum) and with sulfonic acid functions to be modified with electron acceptor groups in order to improve their leaving group

abilities [6–10,112,191,192]. Considerable synthetic efforts were required to prepare intermediates and starting materials which were not yet known [6]; cf. Sections 6.2 and 6.4.

The extensive animal test data which were obtained showed the best of our compounds to be highly active against the murine leukemia model L 1210, the most remarkable feature being high therapeutic indices, i.e. retained activity, but significantly lowered toxicity *vis-à-vis* busulfan **181a** [6]. Among the most promising compounds in our experimental series were the bromomethanesulfonic and chloromethanesulfonic acid analogs of busulfan **181a** and piposulfan **182a**, i.e. **181b**, **181c**, **182b** and **182c** (see Scheme 32) [6], but for mainly commercial reasons the project was terminated before it reached the clinical phase.

$RCH_2SO_2O(CH_2)_4OSO_2CH_2R$

181



182

a, R = H
b, R = Br
c, R = Cl

SCHEME 32

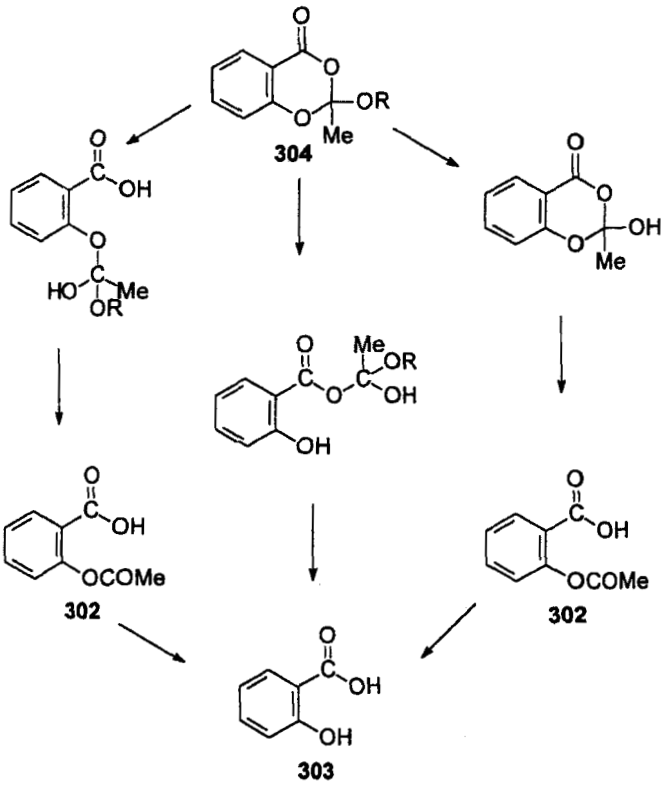
A number of bis(sulfonylformyl)diamines $RSO_2CONH–X–NHCOSO_2R$ **301** were prepared as potential cytostatic agents [191] while a collection of our thiocarbonyl compounds showed marginal antileukemic activity in routine screening [192].

11.1.2. Aspirin Prodrugs

Acetylsalicylic acid (aspirin) **302** [193] is an important drug acting, *inter alia*, as a weak analgesic and as an antiinflammatory agent [194]. Its short (~20 min) *in vivo* half-life suggests a need for a prodrug which could generate **302** *in vivo* by, say, hydrolysis. Earlier attempts in this direction were compromised by the fact that most potential prodrugs released salicylic acid **303** rather than **302** [11,12].

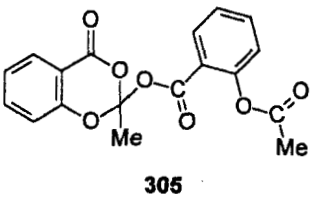
We engaged in an extensive project concerned with the synthesis and hydrolysis of *ortho* esters of the type **304** [11–17]. The majority of the compounds obtained hydrolyzed *in vitro* to salicylic acid **303** rather than to acetylsalicylic acid **302** and the few which did hydrolyze to acetylsalicylic acid **302** did so with rather short half-lives,

incompatible with the requirements for a prodrug; see Scheme 33.



SCHEME 33

A chemically interesting achievement in the course of these studies was, *inter alia*, the preparation and characterization of the unsymmetrical anhydride of acetylsalicylic acid, (*R*,*S*)-2-[(5-hydroxy-4-oxo-4*H*-pyran-2-yl)methoxy]-2-methyl-4*H*-1,3-benzodioxin-4-one **305**; see Scheme 34 [17].



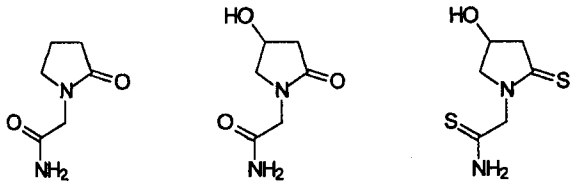
SCHEME 34

11.1.3. Potential Nootropics

Nootropics are a motley group of compounds which are devoid of classical psychopharmacological properties but improve the performance of both the healthy and the damaged brain. Their complete lack of side effects has encouraged their use in spite of their doubtful efficacy which is well established in animal models but considerably

less clear cut in clinical studies [195]. One of the oldest and better-known nootropics is piracetam **306** [196] (together with its second- and third-generation derivatives such as oxiracetam **307** [197]). We reviewed both the biological [18] and the synthetic [20] aspects of the piracetam story. Rumor has it that piracetam is used illegally as a 'smart pill' to improve the intellectual performance of healthy, but stressed, business people such as junior stockbrokers.

As a synthetic contribution to the piracetam family we chose to prepare racemic dithiooxiracetam, i.e. (*R,S*)-4-hydroxy-2-thioxopyrrolidine-1-thioacetamide **308**. It was hoped that this compound might be less hydrophilic than oxiracetam **307** and thus better suited to penetrating the blood–brain barrier; cf. Scheme 35 [19].

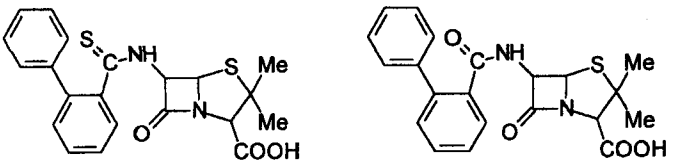


306 **307** **308**

SCHEME 35

11.1.4. Potential Antibiotics

In this miniproject we used the classical antibiotic 6-(*N*-acylamino)penicillanic acids (semisynthetic penicillins) [198] as our departure point and prepared 6-[*N*-(2-phenylthiobenzoyl)amino]penicillanic acid **309** by appropriate thioacylation of 6-aminopenicillanic acid. However, this thio analog of the first-generation, now obsolete, ancillin **310** was devoid of antibiotic properties; see Scheme 36 [199]. Concerning other thiopeptide work of synthetic and biological relevance, see Sections 7.7 and 11.1.3.



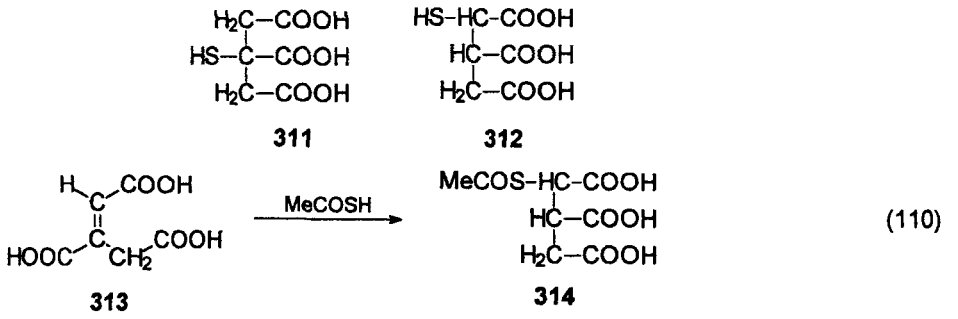
309 **310**

SCHEME 36

11.1.5. Potential Antiarthritic Agents

The value of organic gold(I) compounds, such as the injection drug myocrisin [200] and the orally active auranofin [201], in the therapy of arthritis is well established [202]. We decided to investigate the usefulness of thiocitric acid **311** or thioisocitric acid **312** as a relatively hydrophilic ligand for gold(I) in what it was hoped would be orally active antiarthritic preparations. While attempts to prepare thiocitric acid **311** failed we were able to carry out an anti-Markovnikov addition of thioacetic acid to aconitic acid **313**; see Scheme 37, equation (110). The adduct **314**

could then in a straightforward manner be converted to 1-(aurothio)-1,2,3-propanetricarboxylic acid hydrate **315**, a close analog of myocrisin. Unfortunately, in an adjuvant arthritis animal model **315** proved inactive when given orally. In the same animal model myocrisin and **315** were equipotent when given intramuscularly [203].

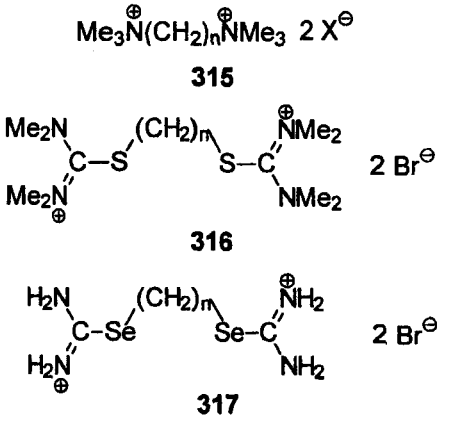


(110)

SCHEME 37

11.1.6. Potential Muscle Relaxants

As a more or less academic exercise we used the well-known *n*-methonium type muscle relaxants **315** and their structure–activity relationships as the starting point [204] and prepared analogous series of bis(*N*,*N*,*N*′,*N*′-tetramethylisothiouronium) salts **316** (from *N*,*N*,*N*′,*N*′-tetramethylthiourea and α,ω-dibromoalkanes) [205] and and bis(isoselenouronium) salts **317** (from selenourea and α,ω-dibromoalkanes [206], respectively. The basic idea was that the more diffuse disposition of the positive charges would make any biological activity less dependent on the length of the central alkylene chain. Unfortunately, neither **316** nor **317** showed any pharmacological properties of interest; see Scheme 38 [205,206].



SCHEME 38

11.2. Potential Pesticides

A portfolio of aryl trichloromethyl sulfides $ArSCCl_3$ **1**, prepared by chlorination of the corresponding aryl methyl sulfides **3**, only exhibited marginal biological activities; cf. Section 1.

A number of *N*-(acetyloligothio)phthalimides were prepared [207] as possible bioisosteres of the fungicide captafol [208]. Sulfur-containing analogs of DDT [209] showed little biological activity [210].

For a collection of marginally fungicidal pentachloroethanesulfenamides, see Section 4.2.2 and Ref. [91].

In a collection consisting of nine new chloro-substituted dithienyl sulfides as well as bis(3,4,5-trichlorothien-2-yl) sulfide, disulfide and trisulfane, all prepared by standard methods, only marginal acaricidal and insecticidal activities were seen [211].

11.3. Occupational Medicine

In this area we provided some chemical expertise to medicinal researchers. Thus, an incident of contact allergy to chlorobis(4-chlorophenyl)methane $(4\text{-}ClC_6H_4)_2CHCl$ was described [212], allergenic acrylic monomers in Nyloprint printing plates were examined [213,214] and the MS behavior of the suspected carcinogen *N*-nitrosodiethanolamine found in cosmetic preparations was investigated (in collaboration with Lars Carlsen, Research Establishment Risø, Denmark) by means of deuterium labeling [215].

12. SERENDIPITY

A significant number of my laboratory's research results were truly serendipitous in the sense that unprecedented compounds were found in reactions which nobody in his or her right mind would have chosen to generate them had they been target molecules.

12.1. 2,3,7,8-Tetrachloro-5,10,11,12-tetrathia-1,4,6,9-tetraazatricyclo[5.3.1.$1^{2,6}$]-dodeca-3,8-diene

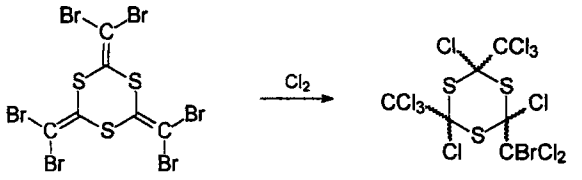
One of the most striking examples is the formation, although in a minuscule yield, of 2,3,7,8-tetrachloro-5,10,11,12-tetrathia-1,4,6,9-tetraazatricyclo[5.3.1.$1^{2,6}$]dodeca-3,8-diene **75** from trichloromethanesulfenyl chloride **2** and ammonia [69]; cf. Section 4.1.1.

12.2. 1,4,4,7-Tetrabromo-1,1,7,7-tetrachloro-2,3,5,6-tetrathiaheptane

Even the most seasoned synthetic chemist would have been hard put to predict that bromodichloromethanesulfenyl bromide $CBrCl_2SBr$ **160** and 1,4,4,7-tetrabromo-1,1,7,7-tetrachloro-2,3,5,6-tetrathiaheptane $CBrCl_2SSCBr_2SSCBrCl_2$ **161** would be the products of the reaction between trichloromethanesulfinic acid **155** and unpurified technical grade thionyl bromide **156** [104]; cf. Section 5.1.

12.3. 2-(Bromodichloromethyl)-2,4,6-trichloro-4,6-bis(trichloromethyl)-1,3,5-trithiane

In an obscure and certainly unexpected reaction chlorination of 2,4,6-tris(dibromomethylene)-1,3,5-trithiane **233** yielded 2-(bromodichloromethyl)-2,4,6-trichloro-4,6-bis(trichloromethyl)-1,3,5-trithiane **318** in a respectable 36% yield [143]:



233 **318** (111)

12.4. Tris(adamantan-1-ylsulfonyl)methane

Our serendipitous synthesis of tris(adamantan-1-ylsulfonyl)methane (cf. Section 5), although not as weird as the two previous examples, is certainly counterintuitive, given our and others' experience with thiophosgene–sulfinate interactions [103].

13. REFUTATIONS

In connection with our keen interest, shared with Kurt Schank (Universität des Saarlandes, Saarbrücken, Germany), in α-oxo sulfones, α-thioxo sulfones and related compounds (cf. Sections 7.4 and 7.5) we could lay to rest old literature claims to the preparation of 'dibenzoyl disulfone' $PhCOSO_2SO_2COPh$ (and of thiobenzoic acid anhydride PhCSOCSPh) [216] as well as of 'sulfurylisatin', i.e. 2,3-dihydrobenzothiazole 1,1-dioxide [217]. Two reported syntheses of tetrabenzoylthiirane did not hold up to our scrutiny either [218]. For our refutation of a claimed synthesis of $C_6H_5SCCl_3$ **1a**, see Ref. [2].

14. SECONDARY LITERATURE

14.1. Textbooks

When my German translation of Lennart Eberson's Swedish textbook in organic chemistry became due for a second edition we decided to revise and expand the German book independently of the Swedish original. This second edition, with its three small volumes [219–221], was used by students minoring in organic chemistry for a considerable number of years before the book went out of print.

14.2. Reference Books

The Nomenclature Committee of the Danish Chemical Society (under my chairmanship) generated the handbook *Kemisk Ordbog* [222], an authoritative source on Danish chemical nomenclature.

In the area of sulfur chemistry I had the privilege of editing two handbook series, *Sulfur in Organic and Inorganic Chemistry* [223–226] and *Topics in Sulfur Chemistry* [227–230].

Two chapters in the handbook *Comprehensive Organic Functional Group Transformations* were entrusted to us [231,232].

14.3. Reviews

Over the years I have authored or co-authored a number of major reviews, i.e. on sulfur-related subjects such as *N*-, *O*- and *S*-trihalomethyl compounds [65], sulfur-containing reagents in organic synthesis [233], reactions of thiocarbonyl compounds with chlorine and with SCl_2 [98], carbon monosulfide [34,35], the chemistry of divinyl disulfides [234], 3-cyanopyridin-2(1*H*)-ones, -thiones and -selones [235], the synthesis of naturally occurring sulfinic acids [236], chlorodithioformates [125], 1,2-dithietes [237], α,β-unsaturated isothiocyanates [238], carbon chloride sulfides [102], geminal disulfenyl dichlorides [101], dithiiranes–thiosulfines [21,239], and on non-sulfur subjects such as piracetam and other structurally related nootropics [18], synthesis and reactions of piracetam-type pyrrolidines [20], 2(5*H*)-furanones [240,241], and a popular account of drug development [242]. A collection of informal, minor reviews deals with the subjects of thiosulfenyl chlorides [243], dithiiranes–thiosulfines [244,245], triphenylmethanethiol–triphenylmethanesulfenyl chloride [246], sulfenyl and selenenyl azides [247], α-thioxo sulfones and *S*-derivatives [248], tetrathioorthocarbonic acid and its derivatives [249], *N*,*N*′-di-*tert*-butylsulfur diimide [250], 1,2,4-thiadiazetidines [251], thio-, seleno- and telluroketenes [141] and thiophosgene *S*-oxide [252].

14.4. Letters to the Editor

On a number of occasions I felt that critical comments were warranted. Thus, I am still mystified by the fact that reputable scientific journals not only permit, but actually demand a lengthy description of standard commercial equipment such as spectrometers in research papers [253], how difficult it appears to be to find an opening clause for a research paper [254], and the appeal of circular arguments [255], and I have also commented on a number of other subjects [256–259]. Also in this category belong my contributions to the *Sulfur Reports* series 'Interesting errors in sulfur chemistry' [71,260–266].

14.5. Editorial Notes

Of the many editorial notes which were part of my work as journal editor the following may still be of some general interest: it is my reply to a hard-luck story from a Third-World chemist who had demanded lower editorial standards for papers from authors with poor experimental and library resources. In my reply I pointed out that a scientific journal is published for the benefit of its readers rather than for that of its authors with no place for hard-luck stories [267].

15. ORGANIC CHEMISTRY AND X-RAY CRYSTALLOGRAPHY

The progress of our research was greatly accelerated by a fruitful symbiosis with X-ray crystallographers who most efficiently contributed crucial structural information. Appropriate thanks are due to Gunadi Adiwidjaja (University of Hamburg, Germany), Vitaly K. Belsky (L. Karpov Institute of Physical Chemistry, Moscow,

Russia), Andreas Fischer (Royal Institute of Technology, Stockholm, Sweden), Alan C. Hazell (Aarhus University, Denmark), Rita Grønbæk Hazell (Aarhus University, Denmark), Carl O. Haagensen (Aarhus University, Denmark), Finn Krebs Larsen (Aarhus University, Denmark) and Inger Søtofte (Technical University of Denmark, Kgs. Lyngby, Denmark).

16. EPILOG

My 40+ years in organic chemistry have been a most enjoyable experience, not only for myself, but also for the many gifted and curious students and research fellows who participated in one or several of my projects. In the many years before it became a common university practice to offer co-authorship to laboratory technicians my laboratory technician Tove Buchholt (née Willum Jensen) contributed decisively to the success of my early work in Århus. It has always been a privilege to watch the fruits of more or less orthodox ideas, lively discussions and hard work by many dedicated people turn into what it is hoped will be widely read and cited journal articles, patents, etc. The breathtaking progress in the sophistication of chemical thinking and experimentation during the same four decades has been another moving and shaking experience.

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While this section does contain a complete bibliography of my life's research, space considerations did not allow every single significant finding to be commented in the text.

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