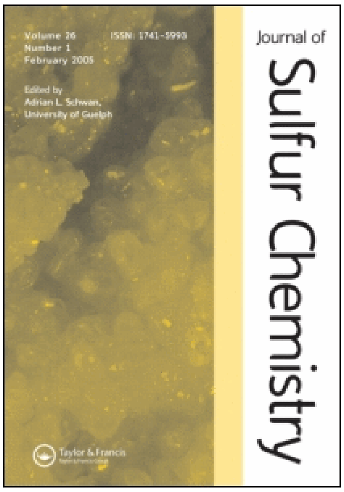

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History of nineteenth-century organosulfur chemistry

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REVIEW

History of nineteenth-century organosulfur chemistry

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A survey of the history of organic sulfur compounds is presented. Mainly, the discoveries that have been achieved on this topic in the nineteenth century are considered. However, outlooks on developments of the twentieth century are given in cases where this seemed meaningful or necessary.

Keywords: organosulfur compounds; history; discovery

1. Introduction

This historical outline of organosulfur chemistry is mainly aimed at the history of the discovery of typical classes of compounds and of particular organic sulfur compounds. Only compounds with direct carbon sulfur bonds are considered. Esters of sulfuric acid ($RO{-}SO_2{-}OR$) or sulfurous acid ($RO{-}SO{-}OR$), and like compounds are not included. Furthermore, sulfur heterocycles are excluded – with a few exceptions such as the fascinating discovery of the fundamental hetarene thiophene, since the host of heterocyclic sulfur compounds would be beyond the scope of this article.

No comprehensive course of history is, therefore, being described. Where it becomes noticeable we will, however, demonstrate that dealing with organic sulfur compounds has gained great significance concerning the general development of theoretical conceptions on the nature and the structure of organic chemical compounds during the period of time between ca. 1800 and 1900. In particular cases, we will also refer to discoveries and developments that have only been achieved in the twentieth century. Furthermore, we will describe the practical importance of organic sulfur compounds, for instance, of certain essential oils. Finally, the typical interrelations between scientific results and the personalities of the involved scientists as well as the style of science in the nineteenth century will be considered, which can be best illustrated by word-for-word quotations from the respective publications.

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2. Carbon sulfides

Carbon disulfide CS_2 [Ger.: *Schwefelkohlenstoff*] can be considered as the simplest sulfur-containing carbon compound – irrespective of the very unstable carbon monosulfide CS which could only be synthesized in the twentieth century. It was first mentioned by Lampadius in 1796. He had more or less accidentally prepared it by heating pyrite (FeS_2) with moist charcoal (*1*). Lampadius called the product which he had obtained *Schwefelalkohol* [sulphuric alcohol]. He and other authors had no distinct idea about the composition of this compound and took it for a compound composed of sulfur and hydrogen or of sulfur, hydrogen and carbon. A synthesis from the elements was first performed by Clément and Désormes in 1802 (*2*). It was achieved by passing sulfur vapor over glowing coals and this is even now the most important technical process for the production of carbon disulfide. The proof of its correct qualitative composition (only sulfur and carbon) is also due to them. Consequently, they named the compound *souffre carburé* (*2*). Occasionally, the literature reads as if Clément and Désormes were the discoverers of carbon disulfide. The authors themselves called their product *eine neue noch unbekannte Verbindung* [a novel still unknown compound], although they conceded in the same paper (*2*): *Uebrigens ist der Schwefel-Kohlenstoff keine durchaus neue Entdeckung, da wir nach Vollendung unserer Arbeit erfahren haben, daß man ihn auch schon anderswo angekündigt hat* [By the way, the sulfur-carbon is not really a new discovery since we have come to know, after the completion of our work, that one has already announced it elsewhere]. As a consequence, their synthesis is, for instance, quoted without the year of publication in the first position of the chapter *Bildung des Schwefelkohlenstoffs* in *Beilsteins Handbuch der organischen Chemie* (*3*). In the following text of the *Beilstein* indeed also a publication of Lampadius (*4*) is quoted – again without the year of its publication. This paper deals, however, with the formation of carbon disulfide *...beim Erhitzen von Kohle mit Schwefelantimon* [... by heating of coal with antimony sulfide] and dates from 1835, whereas no mention is made of Lampadius's original publication of 1796 (*1*). These facts are, however, correctly reported in Gmelin's *Handbuch der anorganischen Chemie* (*5*). The correct quantitative analyses, *15 Teile Kohlenstoff und 85 Teile Schwefel* [15 parts of carbon and 85 parts of sulfur], corresponding with the modern stoichiometric formula CS_2 (15.77% C, 84.23% S), have been reported in 1813 by Berthollet *et al.* (*6*) and independently in 1814 by Berzelius and Marcet (*7*). Berthollet *et al.* were also aware of Lampadius's priority: *Hr. Lampadius hatte im J. 1796, als er Schwefelkiese mit Holzkohle in der Hoffnung destillierte, auf diese Art mehr Schwefel überzutreiben, eine sehr flüchtige Flüssigkeit erhalten, die er Schwefel-Alkohol nannte* [Mr. Lampadius in 1796 had obtained a very volatile liquid, which he called sulfuric alcohol, when he distilled pyrites with charcoal hoping to receive more sulfur] (*6*).

Also the so-called carbon subsulfide C_3S_2 (S=C=C=C=S) has been known since 1893. It is a deep red, very unstable compound which strongly irritates the mucous membranes and tends to polymerize. It was discovered by von Lengyel (*8*), who obtained it by high-temperature pyrolysis of carbon disulfide in an arc. Further solid and insoluble subsulfides of carbon such as C_2S_3 and C_2S_5 have been described in the earlier literature. These are, however, no pure compounds but probably inhomogeneous and undefined mixtures of polymers (*8*).

The history of the discovery of carbon oxide sulfide COS [carbon oxysulfide, carbonyl sulfide] is complicated. Obviously, Couërbe had obtained it as early as 1840 but was not able to identify it correctly. He described the thermal decomposition of alkali and mercury xanthates, which produced among other substances a gas of the composition “COSH” (*9*). He called it xanthin. In 1867, Than obtained impure carbon oxide sulfide by passing carbon monoxide and sulfur vapor through a porcelain pipe at dark red heat or, more convenient and in a pure state, by reaction of potassium thiocyanate with dilute sulfuric acid. He fully characterized it and definitely determined the correct elemental formula COS (*10*). Than (*10*) also discovered the occurrence of carbon oxide sulfide in special Hungarian sulfur springs. Fleischer and Hankó in 1877 stated (*11*):

> . . .so könnte man schliessen, dass Couërbe's . . . Xanthingas aber unstreitig Kohlenoxysulfid gemengt mit etwas Mercaptan und Wasserdampf war. In Betreff des Xanthingases muss ich die in historischer Beziehung interessante Thatsache erwähnen, dass während das Kohlenoxysulfid vor seiner Entdeckung (1867) fast immer als ein Gemenge von Kohlensäure und Schwefelwasserstoff betrachtet wurde, Couërbe im Jahre 1840 diese Verbindung als ein einheitliches, chemisches Individuum, freilich mit nicht richtigen Eigenschaften und Formel beschrieben hat.
>
> [. . .thus one could conclude that Couërbe's . . . xanthin gas doubtlessly was carbon oxide sulfide mixed up with a little mercaptan and water vapour. With respect to the xanthin gas I must make mention of the historically interesting matter of fact that Couërbe has described this compound in 1840 as a homogeneous chemical individual, although with incorrect properties and formula, irrespective of the fact that it was nearly always taken as a mixture of carbonic acid and hydrogen sulfide before his discovery (1867).]

Carbon disulfide and carbon oxide sulfide are analogs of carbon dioxide, and carbon monosulfide is an analog of carbon monoxide. They can therefore well be classed with the inorganic compounds.

3. Organic thiols

Organic thiols (mercaptans), R−SH, are the simplest unequivocally organic sulfur compounds. They were, however, not the first organosulfur compounds that were discovered. Obviously, mercaptans were unknown to the alchemists, although they exhibit striking properties (penetrating smell!) and are formed easily. They are not particularly wide-spread in natural products. The aminoacid cysteine (3-amino-2-sulfanylpropanoic acid, see below) and, in particular, peptides such as glutathione and proteins derived from it are highly important compounds. The presence of thiols as the characteristic constituents in the secretion of the skunk (*Mephitis mephitis*) has only been revealed in 1896 by Aldrich (*12*), after in 1862 Swarts (*13*) had, according to a proposal of Wöhler, performed preliminary studies on this infernally stinking substrate. The exact structure of these thiols, mainly (*E*)-2-butene-1-thiol and 3-methylbutane-1-thiol, and the corresponding *S*-acetates that are also present in the secretion could only be disclosed in 1990 by Wood (*14*).

Thiols are analogs of alcohols. They were early recognized as such and have, in this context, played an important and fundamental role for the development of conceptions about the composition (keyword "type theory") and the systematics of organic compounds.

Ethanethiol (ethyl mercaptan) was the first alkanethiol to be discovered as early as 1833 by Zeise (*15*) who obtained it according to Equation (1) from barium ethyl sulfate and barium hydrogensulfide.

$$(\mathrm{EtO{-}SO_3})_2\mathrm{Ba} + \mathrm{Ba(SH)_2} \rightarrow 2\ \mathrm{Et{-}SH} + 2\ \mathrm{BaSO_4} \qquad (1)$$

Zeise (*15*) coined the name mercaptan, which he derived from (Lat.) *mercurium captans* (*capere* = to seize, *aptus* = affixed) according to the property of this compound to form a characteristic insoluble mercury salt:

> . . .nenne ich den vom Quecksilber aufgenommenen Stoff *Mercaptum* (von: *Corpus mercurio aptum*) und den andern Hydro-Mercaptum, oder besser (theils um keine hypothetische Vorstellung mit der Benennung zu verbinden, theils der Kürze halber) *Mercaptan* (d.h. *Corpus mercurium captans*), wobei ich des Wohllauts wegen, das s fortfallen lasse.
>
> [I call the substance which is taken up by the mercury *Mercaptum* (from: *Corpus mercurio aptum*) and the other one Hydro-Mercaptum, or better (partly in order to avoid a connection between a hypothetical conception and a naming, partly for the sake of shortness) *Mercaptan* (i.e. *Corpus mercurium captans*), whereby I leave out the s because of the euphony.]

Interestingly, Zeise thus made a distinction between the radical C_2H_5S (mercaptum) and the "hydrogen derivative" of this radical C_2H_5SH (mercaptan) and, furthermore, he was reserved with respect to any theoretical statements on the "structure" of the new compound. On the other hand, he recognized the analogy between ethanethiol and ethanol (*15*):

> *Unter allen Umständen verdient gewiß der in Betracht bezogen zu werden,* daß die elementare, also thatsächliche Zusammensetzung des Mercaptans ganz der des Akohols $C^4H^{12}O^2$ entspricht, so daß folglich der Schwefel höchst wahrscheinlich hier, wie bei so vielen Metallverbindungen, die Stelle des Sauerstoffs vertritt.
>
> [In any case, one ought to take into consideration the fact, that the elementary, *i.e*. the real composition of the mercaptan completely corresponds with the one of alcohol $C^4H^{12}O^2$ so that, consequently, the sulfur most probably replaces the oxygen like in many metal compounds.]

Liebig (*16*), as the referee of Zeise's publication (*15*), wrote:

> (Auszug aus der vom Verfasser für die Annalen uns mitgetheilten Originalabhandlung)
> Herr Professor Zeise hat in Schweigger-Seidels Jahrbuch XLI S. 98 und 170 die Entdeckung einiger neuern Schwefelverbindungen mitgetheilt, aus deren ausführlichen Untersuchung zwei bestimmt voneinander unterschiedene neue Körper hervorgegangen sind. Die eine dieser Verbindungen, welche indifferent ist, hat er Thialöl, Thialäther, die andere, welche manche Eigenschaften der Schwefelcyanwasserstoffsäure besitzt, Mercaptan genannt.
> Es ist nun klar, daß wenn der Alkohol als das Hydrat von Kohlenwasserstoff $C_4H_8 + 2H_2O$ mit Wasser betrachtet wird, das Mercaptan eine ähnliche Constitution haben muß: darnach ist es nämlich $C_4H_8 + 2H_2S$...
> Die Mercaptumverbindungen scheinen nun die neue Ansicht von der Constitution des Äthers und Alkohols vollständig zu rechtfertigen. Wir haben in dem Mercaptan eine Verbindung von $C_4H_{12}S_2$, aber 2 Atome Wasserstoff sind darin jedenfalls auf eine andere Art gebunden als die übrigen 10, denn diese 2 Atome Wasserstoff können durch Metalle vertreten werden."
>
> [(Abstract from the original paper which the author has submitted to us for publication in the Annalen)
> Professor Zeise has reported on the discovery of some new sulfur compounds the extensive investigation of which has brought forth two distinctly different new compounds. He has named one of these compounds, which is indifferent, thial oil, thial ether and the second one, which exhibits several properties of thiocyanic acid, mercaptan.
> It is now clear that, if the alcohol is considered as the hydrate of hydrocarbon $C_4H_8 + 2H_2O$ with water, the mercaptan must exhibit a similar constitution, namely $C_4H_8 + 2H_2S$...
> The mercaptum compounds thus seem to justify completely the novel opinion on the constitution of ethers and alcohols. We have got a compound of $C_4H_{12}S_2$ as the mercaptan. But in any case 2 atoms of hydrogen are bound in it in a different way as compared with the other 10, for these 2 atoms of hydrogen can be replaced by metals.]

On page 11 of his report in Zeise's paper (*15*), Liebig (*16*) furthermore commented:

> Über die Zusammensetzung des Thialöls... hat Herr Professor Zeise keine Versuche angestellt; eine Analyse dieser Produkte wäre aber für die Bildung und Constitution des Mercaptans unendlich wichtiger und lohnender gewesen als die außerordentlich weitläuftige Untersuchung der Mercaptide, die darüber keinen Aufschluß geben konnten. Ich glaube Herrn Zeise darauf aufmerksam machen zu müssen, wie sehr seine gediegenen und meisterhaften Untersuchungen durch das Ausspinnen und Beschreiben von Versuchen, die kein Resultat gegeben haben, an Interesse verlieren. Man denke sich jede chemische Verbindung auf die nämliche Art behandelt und die colossalste Geduld wird die Flucht ergreifen.
>
> [Professor Zeise has not performed any experiments... about the composition of the thial oil. An analysis of these products had however been vastly more important and rewarding than the extremely longwinded study of the mercaptides which could not give any information on this topic. I believe I have to call Mister Zeise's attention on the fact, to which extent his solid and masterly investigations lose one's interest through spinning out and describing experiments which did not give any result. Think of every chemical compound being treated in the same way and even the most colossal patience will take to flight.]

Liebig promptly made up for Zeise's omission and described in his publication (*16*) the elemental analysis as well as the correct boiling point of ethanethiol: 36 °C, instead of 63 °C which had been reported by Zeise (*15*). Liebig explained:

> Ich habe in diesem Versuche mehrere Unzen in einer tubulierten Retorte rectificiert, in deren Tubulus ein vortrefflicher Thermometer von Collardeau eingepaßt war.
>
> [I have rectified several ounces in a tubulated retort the tubulus of which was equipped with an excellent thermometer of Collardeau.]

In 1854, Kekulé (*17*) obtained ethanethiol according to Equation (2) from ethanol using phosphorus pentasulfide or phosphorus trisulfide, the reagents he had purposefully prepared.

$$\mathrm{Et{-}OH} + P_4S_{10} \text{ or } P_4S_6 \longrightarrow \mathrm{Et{-}SH} \qquad (2)$$

Kekulé worked in London at that time. He was in close contact with Williamson, whose investigations on the nature of ethers obviously impressed and influenced him. He comprehensively discussed the analogy of mercaptans and alcohols and, moreover, the relationship between thioethers and ethers as well as between thiocarboxylic acids and their functional derivatives and carboxylic acids and their derivatives:

> Außer den Mercaptanen und neutralen Schwefelwasserstoffäthern, die den Alkoholen und Aethern der Wasserreihe entsprechen, müssen demnach auch die den Säuren, wasserfreien Säuren und Säureäthern entsprechenden Gruppen der Schwefelwasserstoffreihe erhalten werden können.
>
> [Besides the mercaptans and the neutral hydrogen sulfide ethers which correspond with the alcohols and the ethers of the water series, also the groups of the hydrogen sulfide series corresponding with the acids, anhydrous acids and acid ethers must thus be obtainable.]

Consequently, Kekulé (*17*) also described the preparation of such analogs in the above-mentioned publication.

Methanethiol (methyl mercaptan) was prepared in a pure form (*Methylsulfhydrat*) only in 1887, b.p. 5.8 °C, and definitely characterized by Klason (original Svedish spelling: Claesson) at the university of Lund. Klason (*18*) prepared it according to Equation (3) from sodium methyl sulfate and potassium hydrogen sulfide.

$$\mathrm{MeO{-}SO_3Na + KSH \longrightarrow Me{-}SH + KNaSO_4} \tag{3}$$

Earlier reports of Gregory (*19*) and of Obermeyer (*20*) turned out to be inadequate according to Klason (*18*). The substances which these authors had obtained according to Equation (4) exhibited a boiling point of 21°C and consisted mainly of dimethyl sulfide.

$$\begin{aligned}&\mathrm{MeO{-}SO_3M + KSH \longrightarrow Me{-}SH(?) + KMSO_4} \\ &\mathrm{M = K, Ca_{1/2}}\end{aligned} \tag{4}$$

Klason wrote in his paper (*18*):

> Da es immer wünschenswert ist, das einfachste Glied einer ganzen Körperklasse zu kennen, habe ich diese Verbindung und einige seiner Verbindungen in reiner Form dargestellt. Aus dieser Untersuchung, die allerdings größere Unannehmlichkeiten und Schwierigkeiten mit sich trug, als ich anfangs dachte, ging zunächst hervor, dass Gregory nur ein mit Methylsulfhydrat verunreinigtes Methylsulfid in Händen hatte.
>
> [Since it is always desirable to know the simplest member of a series of compounds I have prepared this compound and some of its derivatives in a pure state. It turned out from this study, which caused however worse troubles than I could think of at the beginning, that Gregory had only had methyl sulfide contaminated with methyl sulfhydrate in his hands.]

Klason mentioned that methyl mercaptan, ethyl mercaptan, propyl mercaptan and butyl mercaptan were the well known sulfhydrates.

Methanethiol is formed during the decay of proteins by anaerobic bacteria as Nencki (Nencki's original publications on this topic are not easily accessible but they have been literally reproduced in a complete edition) (*21*) found out by comprehensive investigations. In 1889, Nencki (*22*) and his brother Nencki (*23*) detected it in the intestinal winds. In 1891, Nencki (*24*) also "found" it in the distillate of the characteristically smelling urines which every other human being excretes after the consumption of asparagus. But obviously he had only detected a hydrolysis product according to a re-examination, which has been performed in 1975 with modern analytical methods (*25*). White found each 2–5 mg of *S*-methyl thioacrylate and *S*-methyl 3-(methylthio)propanethioate but no methanethiol in urines after the consumption of 100 g of asparagus. He wrote (*25*):

> The odor-bearing compound was tentatively identified as methanethiol in 1891 by Nencki who distilled the urines of four individuals who had eaten a total of 7 kg of asparagus (1) (*24*). Identification was based on the odor of the distillate and precipitation of mercury and lead mercaptides... Although S methyl thioacrylate and S-methyl

> 3-(methylthio)thiopropanoate have been identified as the odor-causing compounds, their metabolic origin remains an open question.

Prop-2-ene-1-thiol (allyl mercaptan) is of particular importance for the organosulfur chemistry because the disulfides and oligosulfides in garlic and onion oil are derived from it (see below). The allylsulfanyl residue is also a constituent of allyl thiocyanate, which is the isomer of the long known mustard oil (allyl isothiocyanate, see below). Prop-2-ene-1-thiol was prepared in 1857 by Cahours and Hofmann (*26*) using the standard method (Equation (5)).

$$\mathrm{CH_2 = CH{-}CH_2\text{-}I + KSH \longrightarrow CH_2 = CH{-}CH_2\text{-}SH + KI} \tag{5}$$

The authors comprehensively discussed the remarkable allyl residue which, for the first time, had been found as a constituent of naturally occurring sulfur compounds. They synthesized all simple functional allyl derivatives that were unknown at that time such as allyl ethers, allyl esters, allyl amine, allylurea, allyl cyanate, allyl xanthate, and, in particular, allyl alcohol, the *Mittelpunkt der Allylkörper* [the center of the allyl bodies] as well as allyl mercaptan. They pointed out that these compounds are fully equivalent with the corresponding functional ethyl derivatives:

> Der Geruch . . . Dieß gilt in der That von fast sämmtlichen Allylverbindungen; sie riechen wie die entsprechenden Aethylverbindungen, nur etwas stechend senfartig.
>
> [The odor . . . This is really true for nearly all allyl compounds; they smell as the corresponding ethyl compounds do, but a bit pungently mustard-like.]

and furthermore:

> Es bedarf nur eines vergleichenden Blicks auf die Formeln der Propylenverbindungen und des Senf- und Knoblauchöls:. . ., um zu sehen, daß sich in allen diesen Verbindungen ein gemeinschaftliches Radical – C_6H_5, (*27*) Allyl – annehmen läßt. Diese Beziehung ist Herrn Reynolds* (*28*) nicht entgangen und er führt in seiner schon vor sechs Jahren veröffentlichten Abhandlung namentlich an, daß man wahrscheinlich das Knoblauchöl und das Senföl mittels Schwefel- und Schwefelcyankalium aus den Propenylverbindungen künstlich werde erhalten können.
>
> [It only needs a comparative look at the formulae of the propenylic compounds and at the garlic and mustard oils to recognize that one can assume a common radical – C_6H_5, (*27*) allyl – in all these compounds. This relation has not escaped Mr. Reynold's* (*28*) notice and he particularly mentions that one probably would be able to prepare synthetically garlic and mustard oil from the propenylic compounds and potassium sulfide or thiocyanate.]

Cahours and Hofmann (*26*) particularly appreciated the scientific results of Reynolds (*28*), Will (*29*), Wertheim (*30*), and of Berthelot and de Luca (*31*) on the constituents of garlic and mustard oil.

> In engem Zusammenhange mit diesen Forschungen stehen die schönen Versuche von Will und von Wertheim über die ätherischen Oele der schwarzen Senfs und des Knoblauchs, welche, obwohl scheinbar einem ganz verschiedenen Felde zugewendet, nichtsdestoweniger auf eine unzweideutige Beziehung dieser Oele zu den Körpern der Acrylreihe hinwiesen. Diese Beziehung ist durch neuere Untersuchungen von Berthelot und de Luca in ein klareres Licht getreten.
>
> [. . . the nice experiments of Will and of Wertheim are closely connected with these investigations about the etheric oils of black mustard and garlic which, although devoted to quite a different field, nevertheless indicate an unambiguous relation of these oils with the bodies of the acrylic series. This relation has been clearly brought to light by recent investigations of Berthelot and de Luca.]

They explicitly disclaimed the preparation of allyl isothiocyanate (mustard oil, see Isothiocyanates, Section 9) because of Berthelot and de Luca's (*31*) priority. On the other hand, they described besides the preparation of allyl mercaptan that of diallyl sulfide, which they found undistinguishable in its smell and all its chemical properties from natural garlic oil. They dropped their first idea to classify the propenylic compounds with the acrylic series and wrote instead:

> . . . so ziehen wir vor, die ursprünglich von Will und Wertheim vorgeschlagenen Nomenclatur beizubehalten. Der Name Allyl ist auch bereits in mehreren andern Abhandlungen, welche seit der Veröffentlichung der gedachten Notiz erschienen sind, angewendet worden.

> [. . . thus we prefer to retain the nomenclature originally proposed by Will and Wertheim. The name allyl has also been already used in several other articles which have appeared since the publication of the note thought of.]

Thioglycollic acid (sulfanylethanoic acid) was first described by Carius (*32*), who prepared it according to Equation (6), and wrote:

> . . . ergiebt sich die Darstellungsweise dieser Sulfosäure und ihrer Homologen fast von selbst; sie entsteht beim Erhitzen einer concentrirten Lösung von monochloressigsaurem Kalium mit Kaliumsulfhydrat. . .

> [. . . the method of preparation for this sulfoacid and its homologues follows nearly as a matter of course. It forms by heating a concentrated solution of potassium monochloroacetate with potassium sulfhydrate. . .]

$$\mathrm{Cl{-}CH_2{-}COOK + KSH \longrightarrow HS{-}CH_2{-}COOH + KCl} \tag{6}$$

Later on, Claesson (Klason) (*33*) prepared pure sulfanylacetic acid as well as quite a number of its salts and esters. He showed that Carius's substance mostly consisted of sulfide, thiodiethanoic acid [$S(CH_2{-}COOH)_2$], because he had applied unsuitable reaction conditions. Wislicenus (*34*) in 1865 synthesized pure ethyl sulfanylethanoate (*Mercaptoglykolsäureether*) from ethyl chloroacetate and potassium hydrogen sulfide. He was able to separate the by-product and identify it as the corresponding sulfide.

In the twentieth century, thioglycollic acid has become very important for the praxis of hair cosmetics. It is able to break, in a redox reaction, the cystine disulfide bridges of the keratin, which give the shape and the firmness to the hair. Thereby the cystine residues are transformed into cysteine residues. The rigidity of the hair is lost and it can be laid into a new trim. In the final fixation process, the cysteine residues are re-oxidized to cystine disulfide bridges. The result is a permanent wave.

Thiolactic acid [2-sulfanylpropanoic acid, CH_3-CH(SH)-COOH], the homolog of sulfanylethanoic acid, was prepared in 1864 by Schacht from sodium chloroacetate and potassium hydrogen sulfide (*35*). He separated the pure compound from the obligate by-product by a labourious procedure *via* the lead and barium salts. According to Claesson, this by-product, once more, was the corresponding sulfide 2,2'-thiodipropanoic acid $S(CHMe{-}COOH)_2$ (*33*).

Thiophenol, the sulfur analog of phenol and prototype of the aromatic thiols, was first described in 1861 by Vogt who named it (Ger.:) *Benzylmercaptan* because the name phenyl for the C_6H_5-residue was not yet generally established at that time and benzyl was used instead. He obtained it by reduction of benzenesulfonyl chloride (Ger.: *Benzylsulfonchlorid*) according to Equation (7) or by reduction of diphenyl disulfide (Ger.: *Zweifach Schwefelbenzyl*) with zinc in sulphuric or hydrochloric acid according to Equation (8) (*36*).

$$\mathrm{Ph{-}SO_2{-}Cl + Zn/H_2SO_4 \longrightarrow Ph{-}SH} \tag{7}$$

$$\mathrm{Ph{-}S{-}S{-}Ph + Zn/HCl \longrightarrow 2\ Ph{-}SH} \tag{8}$$

This is a typical example for the preparation of an aromatic thiol by a reductive process which plays a less important role in the aliphatic series, although Vogt (*36*) has also prepared ethanethiol in this way. The direct displacement of a phenolic hydroxy group by a thiol group is rare. Kekulé (*37*) has, however, prepared thiophenol by sulfurising phenol with phosphorus pentasulfide in analogy with the aliphatic thiols, Equation (9).

$$\mathrm{Ph{-}OH + P_4S_{10} \longrightarrow Ph{-}SH} \tag{9}$$

He characterized it as *identisch mit dem von Vogt entdeckten Benzylmerkaptan* [identical with benzyl mercaptan discovered by Vogt] and further on wrote:

> Die mitgetheilten Versuche setzen ausser Zweifel, dass das sogenannte Benzylmercaptan das wahre Thiophenol, d. h. die dem Phenol entsprechende Schwefelverbindung ist, sie zeigen ausserdem, dass alle schwefelhaltigen Substanzen, die man seither aus Benzol dargestellt hat, auch aus Phenol erhalten werden können.

> [The reported experiments put it beyond doubt that the so called benzyl mercaptan is the real thiophenol, *i.e.* the sulfur compound corresponding to phenol, they also show that all sulfur containing substances, which have since been prepared from benzene, may also be obtained from phenol.]

Diphenyl disulfide was also transformed into potassium thiophenolate and potassium benzenesulfinate by disproportionation with potassium hydroxide by Schiller and Otto (Equation (10)) (*38*):

$$2\ \mathrm{Ph{-}S{-}S{-}Ph} + 4\ \mathrm{KOH} \longrightarrow 3\ \mathrm{Ph{-}SK} + \mathrm{Ph{-}SO_2K} + 2\ \mathrm{H_2O} \tag{10}$$

Furthermore, Otto also obtained thiophenol by reduction of benzenesulfonyl chloride with zinc *via* the intermediates zinc benzenesulfinate and diphenyl disulfide (*39*). This is one of today's standard procedures for the preparation of thiophenols. Benzenesulfonyl chloride (*40*) as well as diphenyl disulfide (*41*) can also be advantageously reduced to thiophenol by electrolysis instead of using zinc metal.

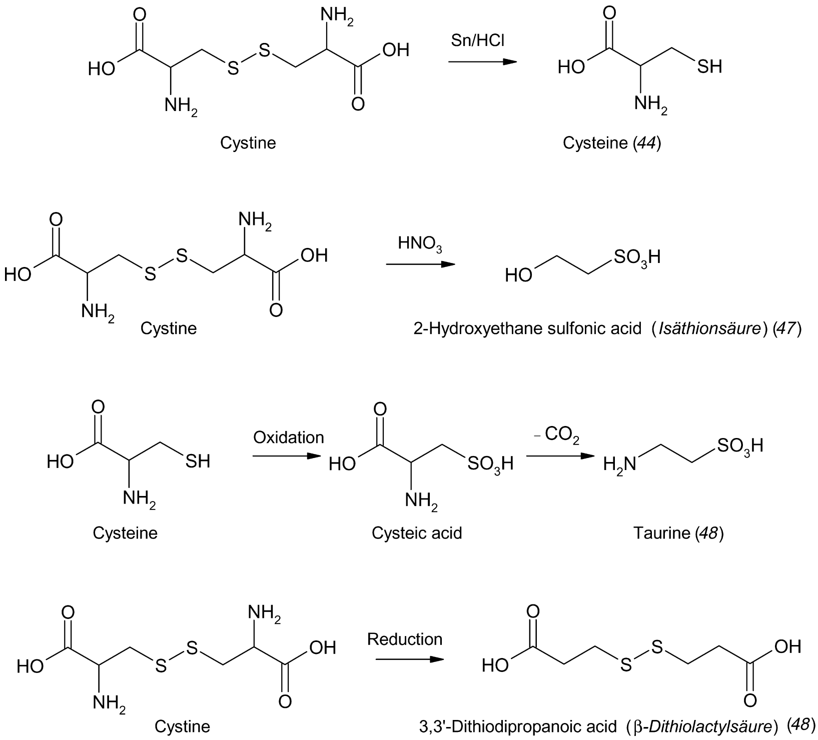
Friedel and Crafts (*42*) obtained thiophenol by a completely different method. They prepared it by electrophilic substitution of benzene with sulfur dichloride or elemental sulfur in the presence of aluminium trichloride and subsequent hydrolysis (Equation (11)).

$$\mathrm{PhH} + \mathrm{SCl_2}\ \text{or}\ \mathrm{S_8} + \mathrm{AlCl_3} \xrightarrow{(\mathrm{H_2O})} \mathrm{Ph{-}SH} \tag{11}$$

During these reactions, also thianthrene and diphenyl disulfide were formed as by-products besides thiophenol. Finally, Leuckart (*43*) applied arenediazonium salts as starting material. He obtained arenethiols by treating these salts with potassium xanthate and hydrolysis of the intermediately formed *S*-aryl dithiocarbonates with alkali (Equation (12)). This reaction also developed into a standard method for the preparation of arenethiols.

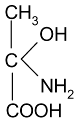
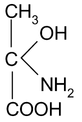
$$\begin{aligned} &\mathrm{Ar{-}N_2^+Cl^-} + \mathrm{EtO\text{-}CS\text{-}SK} \longrightarrow \mathrm{Ar{-}S{-}CS{-}OEt} + \mathrm{N_2} + \mathrm{KCl} \\ &\mathrm{Ar{-}S{-}CS{-}OEt} + \mathrm{KOH} \longrightarrow \mathrm{Ar{-}SK} + \mathrm{EtOH} + \mathrm{COS} \end{aligned} \tag{12}$$

Cysteine [2-amino-3-sulfanylpropanoic acid, $\mathrm{HS{-}CH_2{-}CH(NH_2){-}COOH}$], the important building block of the proteins, is, as mentioned above, one of the not too frequently naturally occurring thiols. It was first prepared by Baumann (*44*) who obtained it by reduction of cystine (therefrom its name cysteine, see below) with tin in hydrochloric acid (Scheme 1). Mostly, the oxidized form cystine occurs in proteins and can be easily isolated in useful amounts. Baumann (*45*) assigned the incorrect structure of α-amino-α-sulfanylpropanoic acid, $\mathrm{CH_3\text{-}C(NH_2)(SH)\text{-}COOH}$, to cysteine because he had obtained ammonium pyruvate $[\mathrm{CH_3\text{-}CO\text{-}CO_2^-}][\mathrm{NH_3^+}]$ by its oxidation with diammine-silver(I), although his consequent attempts to prepare cysteine from α-alanine had been unsucessful. In 1902, Neuberg disproved this result and showed that the two functional groups are linked to different carbon centers because cystine is oxidized to 2-hydroxyethanesulfonic acid (*Isäthionsäure*) with nitric acid (Scheme 1), which Carius (*46*) had already prepared by oxidation of *Aethylenmonosulfhydrat*, $\mathrm{HS\text{-}CH_2\text{-}CH_2\text{-}OH}$, with nitric acid and characterized in 1862. Neuberg (*47*) could, however, not decide between the two regioisomers $\mathrm{HS{-}CH_2{-}CH(NH_2){-}COOH}$ and $\mathrm{H_2N{-}CH_2{-}CH(SH){-}COOH}$. This task was left to Friedmann who obtained taurine, $\mathrm{H_2N{-}CH_2{-}CH_2{-}SO_3H}$, by oxydation of cysteine (*Proteid Cystein*), and 3,3'-dithiodipropanoic acid (*β-Dithiolactylsäure*) by reductive elimination of ammonia from cystine (Scheme 1). In this way, he proved that the sulfur is linked to the β-position (*48*).



Scheme 1.

In consideration of Friedmann’s results (*48*), Erlenmeyer Jr. finally answered the question of the correct structures of cysteine and cystine in 1903 and 1904. He wrote (*49*):

> Merkwürdiger Weise wurden diese Formeln lange Zeit hindurch als unumstritten richtig angenommen, ja sogar noch im Jahre 1901 hat Kossel[16] (*50*) auf Grund der Baumann’s chen Cysteinformel die Formel des Serins abgeändert in:
>
> 
>
> $$\begin{array}{l} CH_3 \\ | \\ C\genfrac{}{}{0pt}{}{\diagup OH}{\diagdown NH_2} \\ | \\ COOH \end{array}$$
>
> obwohl doch Cramer durch Ueberführung des Serins in Glycerinsäure gezeigt hatte, dass im Serin Hydroxyl- und Amidogruppe nicht an ein und demselben Kohlenstoffatome stehen können. . .
> Da nun Cystin bei vorsichtiger Oxydation Cysteinsäure liefert, in welcher der Schwefel des Cystins in die Sulfogruppe übergeführt ist und da diese Cysteinsäure unter Kohlensäureverlust in Taurin, . . .übergeht, so folgt für die Cysteinsäure die Formel: . . . für das Cystein und Cystin aber die Formeln:. . .”
>
> [Strangely enough, these formulae have been taken as undisputably correct for a long time. As recently as in 1901 Kossel[16] (*50*) has even changed the formula of serine to
>
> 
>
> $$\begin{array}{l} CH_3 \\ | \\ C\genfrac{}{}{0pt}{}{\diagup OH}{\diagdown NH_2} \\ | \\ COOH \end{array}$$
>
> on account of Baumann’s formula of cysteine although Cramer did show by transformation of serine into glyceric acid that the hydoxy and the amino groups cannot be at the same carbon atom. . .
> But since cysteine gives cysteic acid on mild oxidation, in which the sulfur of the cysteine is transformed into a sulfo group and since this cysteic acid gives taurine under loss of carbonic acid one can conclude the following formulae for cysteic acid, cysteine and cystine. . .]

Erlenmeyer (*49*) once more pointed out that an analogy exists between corresponding oxygen and sulfur compounds and wrote:

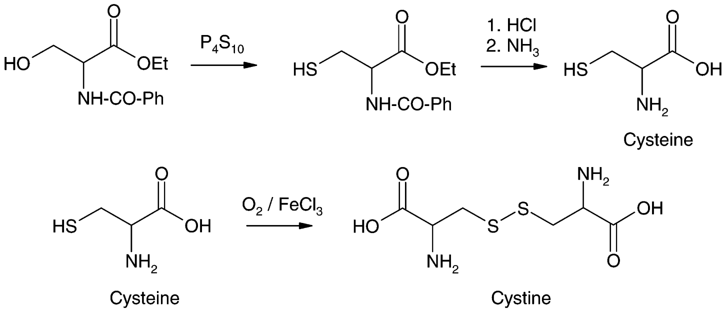
> . . . tritt eine große Uebereinstimmung mit der Formel des Serins auf, $C_3H_7NO_3$, d. h. man konnte daran denken, dass Cystin nichts anderes sei als Serin, in welchem ein Sauerstoffatom durch Schwefel vertreten ist und thatsächlich hat bereits Cramer[13] (*51*) im Jahre 1865 dieser Meinung Ausdruck verliehen, indem er Cystin mit dem Alanin und Serin in eine Reihe geschrieben hat: . . .. ohne aber diese Beziehung experimentell beweisen zu können. . ..
> Auch für den von Cramer geäußerten Zusammenhang zwischen Cystin und Serin hat Friedmann den Beweis erbracht, indem er aus der Cysteinsäure durch Vertretung der Sulfogruppe gegen Hydroxyl Serin erhielt . . ..

> [. . . a striking agreement with the formula of of serine, $C_3H_7NO_3$, exists, *i.e.* one could think of cysteine to be nothing else but serine in which an oxygen atom is substituted by sulfur and, as early as in 1865, Cramer[13] (*51*) has indeed given utterance to this fact by writing cystine together with alanine and serine in a series: . . ., however without being able to prove this relation experimentally. . .
> Friedmann has also proved Cramer's opinion on the relation between cystine and serine by obtaining serine from cysteic acid through substitution of the sulfo for a hydroxy group. . .]

Cramer (*51*) had, however, proceeded on a formula of cystine which in fact was due to cysteine. He thereby followed Gmelin (*52*) whose assumption had been based on a slightly incorrect elemental analysis of cystine although Thaulow (*53*) had already reported the correct formula and also Baumann (*44*, *45*) had proved the difference between the thiol cysteine and the disulfide cystine. Erlenmeyer was aware of this and explicitly clarified the redox relationship between cysteine and cystine on account of his own investigations. As a highlight, Erlenmeyer performed a total synthesis of the two compounds. In consideration of the structural analogy of serine and cysteine, on which he had laid emphasis, he used ethyl *N*-benzoylserinate as starting compound and obtained cysteine in two steps and finally cystine by air oxidation of the cysteine (Scheme 2). In conclusion, he remarked (*49*):

> Der einzige Unterschied des synthetischen und des natürlichen Productes [Cystin aus menschlichem Haar] ist der, dass die Lösung des ersteren die Ebene des polarisierten Lichtes nicht dreht.

> [The only difference of the synthetic and the natural product [cystine from human hair] lies in the fact that a solution of the former does not rotate the plane of polarised light.]



Scheme 2.

Shortly after that, Gabriel (*54*) prepared the above-mentioned isomers $H_2N{-}CH_2{-}CH(SH){-}CO_2H$ (Isocystein) and $[H_2N{-}CH_2{-}CH(CO_2H){-}S\text{-}]_2$ (Isocystin) through an unambigous synthesis from β-alanine.

Cysteine often plays a specific role in peptides such as glutathione because it easily undergoes physiologically important redox reactions. The typical disulfide bridges that emerge under the formation of cystine are of great importance for the proteins because they are responsible for their conformation (tertiary structure) and thus for their functionality (see above, permanent wave). In addition, the strong nucleophilicity of the thiol group of cysteine is of physiological significance.

It enables the glutathione to form water-soluble conjugates. In this way, the epoxides of arenes, such as benzene and benzo[a]pyrene which exhibit a high carcinogenic activity are detoxicated.

4. Organic sulfides and disulfides

Organic sulfides (sulfanes, thioethers) are formally derived from ethers by displacement of the oxygen by sulfur or, from a different point of view, by substitution of the two hydrogen atoms of hydrogen sulfide by two organic residues. This analogy of the sulfur with the oxygen compounds has been recognized from the beginning and it has been claimed as a proof of the type theory (see above).

Dimethyl and diethyl sulfide, the simplest thioethers, were prepared and characterized in 1840 by Regnault. They were obtained by a nucleophilic displacement reaction of the corresponding chloroalkanes with potassium sulfide (Equation (13)) (*55*):

$$2\ \mathrm{R{-}Cl} + \mathrm{K_2S} \longrightarrow \mathrm{R{-}S{-}R} + 2\ \mathrm{KCl} \qquad (13)$$

$$\mathrm{R} = \mathrm{Me, Et}$$

A previous first hint on diethyl sulfide was given by Döbereiner (*56*) who described its formation by reaction of iron or antimony sulfide with hydrogen chloride and ethanol (Equation (14)). Later on, Klason prepared diethyl sulfide by alkylation of potassium sulfide with sodium ethyl sulfate (Equation (15)) (*18*, *57*).

$$\mathrm{FeS\ (or\ Sb_2S_3)} + 2\ \mathrm{HCl} + 2\ \mathrm{EtOH} \xrightarrow{\Delta} \mathrm{Et\text{-}S\text{-}Et} + \mathrm{FeCl_2} + 2\ \mathrm{H_2O} \qquad (14)$$

$$2\ \mathrm{EtO\text{-}SO_3Na} + \mathrm{K_2S} \longrightarrow \mathrm{Et\text{-}S\text{-}Et} + 2\ \mathrm{KNaSO_4} \qquad (15)$$

According to Abel (*58*), diethyl sulfide is also formed by heating of the urine of dogs with potassium hydroxide. It results from the decomposition of diethyl methyl sulfonium salts $\mathrm{Et_2SMe^+X^-}$ which are among the constituents according to Neuberg and Grosser (*59*).

Bis(2-chloroethyl)sulfane (dichlorodiethyl sulfide) had obviously been formed, although in an impure form, when as early as 1822 Despretz (*60*) studied the reaction of sulfur dichloride with ethene. Later on, Niemann (*61*) performed the same addition reaction and obtained a product which, according to its elemental analysis, mostly consisted of the corresponding disulfide. But obviously, it also contained a significant amount of the sulfide since Niemann already recognized the dangerous properties of this notorious thioether and mentions:

> Die . . . Flüssigkeit zeigt nun einen sehr eigenthümlichen, unangenehmen, an Meerrettig erinnernden, die Geruchsnerven aufreizenden Geruch . . . Die charakteristischste Eigenschaft dieses Oeles ist zugleich eine sehr gefährliche. Sie besteht darin, daß selbst die geringste Spur, die zufällig auf irgendeine Stelle der Haut kommt, anfangs zwar keinen Schmerz hervorruft, nach Verlauf einiger Stunden aber eine Röthung derselben bewirkt und bis zum folgenden Tage eine Brandblase hervorbringt, die sehr lange eitert und außerordentlich schwer heilt, unter Hinterlassung starker Narben, — eine Wirkung, welche dieser Körper auf gleiche Weise bei verschiedenen Individuen hervorbrachte. Es ist deshalb auch beim Arbeiten mit demselben große Vorsicht erforderlich.
>
> [The . . . liquid now exhibits a very particular, unpleasant odor which resembles horseradish and irritates the olfactory nerves . . . The most characteristic property of this oil is, at the same time, a very dangerous one. It consists in the following. Even a minimum trace accidentally contacting any part of the skin, although not causing pains in the beginning, is producing a reddening after a couple of hours and a blister the next day, which is festering for a long time. It is healing only with extraordinary difficulties and will leave heavy scars. The compound caused these effects to different individuals. Careful precautions are therefore necessary while working with it.]

Guthrie (*62*) treated ethene with sulfur dichloride in the same way as Niemann (*61*) did. He made the same observations, although his product exhibited analytical figures close to the composition of 2-chloroethanesulfenyl chloride $\mathrm{Cl{-}CH_2{-}CH_2{-}S{-}Cl}$.

Dichlorodiethyl sulfide, which was comprehensively studied in 1886 by Meyer (*63*), has gained a particularly tragic significance in the twentieth century. It has been applied as a chemical warfar agent [Mustard Gas, Yperite (called after the city of Ypern in Belgium, where during the night of 11/12 July 1917, this chemical was used for the first time as a chemical weapon by the German army in World War I), Lost (called after the German chemists *Lo*mmel and *St*einkopf), Yellow Cross] (*64*). It was then banned (*65*) and, remarkably, not used again in World War II – as far as one knows. But nevertheless it was further on produced for the arsenals and brought into action again in armed conflicts, for instance in 1984 during the war between Iran and Iraq (*66*).

Meyer, the discoverer of thiophene (see below), prepared bis(2-chloroethyl)sulfane $(Cl{-}CH_2{-}CH_2)_2S$ from 2-chloroethanol according to Equation (16). His aim was to synthesize the six-membered analog of thiophene from it by use of diethyl malonate.

$$\begin{aligned} &2\ Cl{-}CH_2{-}CH_2{-}OH + K_2S \longrightarrow (HO{-}CH_2{-}CH_2)_2S \\ &(HO{-}CH_2{-}CH_2)_2S + PCl_3 \longrightarrow (Cl{-}CH_2{-}CH_2)_2S \end{aligned} \qquad (16)$$

Surprisingly, he does not mention the earlier results on the compound, not even Niemann's observations (*61*) on its dangerous nature. He wrote about the intermediate thiodiglycol, which he had obtained according to Carius's procedure (*63*):

> Ich glaube aber, dass dieser Forscher den durch ihn beschriebenen Körper garnicht als solchen unter den Händen gehabt hat, denn die Eigenschaften, die er angiebt, sind ganz andere, als die, welche ich beobachtet habe. Carius^1 (*46*) beschreibt die Substanz als in Wasser unlösliche Krystalle, während ich sie als Oel erhielt, das — wie bei einem Glykol zu erwarten — mit Wasser in allen Verhältnissen mischbar ist.
>
> [I believe, however, that this scientist has not at all had this body, which he has described, in his hands since the properties which he claims are completely different from those which I have observed. Carius^1 (*46*) describes the substance as crystals, completely insoluble in water, whereas I obtained it as an oil which — as one would expect of a glycol — is miscible with water in all ratios.]

He described the dichloro compound as: . . . *ein in Wasser untersinkendes und damit nicht mischbares Oel von schwachem, süsslichem, nicht unangenehm ätherartigem, nur wenig an Schwefelverbindungen erinnernden Geruch. In Eiswasser gestellt, erstarrt es zu zolllangen Prismen. Es siedet unter geringer Zersetzung bei* 217 °*C.* [. . . an oil sinking in water and not miscible with it, exhibiting a faint, sweetish odor, which is not unpleasantly ether-like and only slightly resembling of sulfur compounds. After putting it into ice-water it solidifies to form inch long prisms. It boils under slight decomposition at 217 °C].

The desired thiophene analog was, however, not obtained from this dichloride. Instead, Meyer (*63*) alarmedly wrote:

> Die beabsichtigten Arbeiten mit diesem Chloride sind nicht fortgeführt worden, einerseits weil, wie die nachstehende Arbeit des Hrn. Krekeler (*67*) zeigt, das erstrebte Ziel nicht erreicht worden ist, andererseits aber wegen der äußerst giftigen Eigenschaften des Körpers, welche zunächst eine Untersuchung desselben in physiologischer Richtung veranlassten. Es ist höchst auffallend, dass diese anscheinend so harmlose Substanz, welche wenig flüchtig, in Wasser fast unlöslich, von sehr schwachem Geruche und ganz neutraler Reaction ist und welche auch nach ihrer chemischen Constitution keineswegs aggressive Eigenschaften erwarten lässt, eine specifisch toxische Wirkung ausübt. Gegen diese scheinen verschiedene Personen sehr verschieden empfindlich zu sein. Ich selbst habe beim andauernden Arbeiten mit dem Körper, ohne dass ich irgend welche Vorsicht anwandte, keine Belästigung verspürt. Dagegen zeigten sich bei einem Praktikanten, welcher die Verbindung darstellte, starke Hautausschläge und eine bald vorübergehende Augenentzündung. . . Ich war anfangs geneigt, die an dem Chlorid beobachteten Wirkungen auf besondere Empfindlichkeit eines Einzelnen zurückzuführen, aber ich wurde eines Besseren belehrt durch Versuche, welche auf meine Bitte im hiesigen physiologischen Institute angestellt wurden. Nach diesen hat die Substanz in hohem Maasse gefährliche Eigenschaften, wie die folgenden vorläufigen und sich auf das anscheinend wichtigste beschränkenden Mitteilungen lehren. . .
>
> [The intended experiments with this chloride were not continued because, on the one side, the desired aim was not achieved, as the following paper of Mr. Krekeler (*67*) will demonstrate and, on the other hand, because of the extremely poisonous properties of the body, which primarily caused its investigation under physiological objectives.

> It is most striking that this seemingly harmless compound, which is little volatile, nearly insoluble in water, of only faint odor and completely neutral in its reactions, and which according to its chemical constitution is not at all expected to exhibit aggressive properties, should produce a specific toxic activity. Different persons seem to be of very different sensitiveness to it. I myself have not perceived any inconveniences during continuous work with this body, although I did not take any precautions. However, a student who prepared the compound suffered heavy skin eruptions and a temporary inflammation of the eye... At the beginning I was prepared to attribute the observed activity of the chloride to the peculiar sensitiveness of an individual but I was set right by experiments which were performed at my request at the physiological institute in this town. According to them, the substance exhibits highly dangerous properties as demonstrated by the following preliminary communications, which are confined to the most obvious and important aspects...]

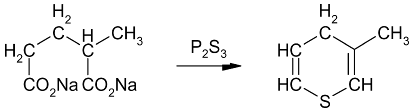
The corresponding animal experiments were performed with rabbits (*63*, *68*). They clearly demonstrated that the compound represents a dangerous poison. It leads to death under the heaviest symptoms, which Meyer (*68*) insistently described in his publications. He also found out that the monochloro derivative $EtS-CH_2-CH_2-Cl$ exhibits similar but less dramatic toxic effects whereas diethyl sulfide is non-toxic. As a consequence, he wrote:

> Da die Dämpfe des Chlorids auch auf die mit vorstehend kurz berichteten Versuchen Beschäftigten ähnlich nachtheilige Wirkung äusserten, so mussten diese Versuche abgebrochen werden.
> Es scheint, dass das Chlorid seine heftig reizenden Wirkungen wenigstens ganz vorwiegend erst nach Aufnahme ins Blut entfaltet.
> ... dass Kaninchen nach kurzem Einathmen der Dämpfe des Chlorids regelmässig an Pneumonie zu Grunde gehen, und weiter, dass bei Aufpinselung einer Spur des Oels auf das Ohr heftige Entzündung der Ohren und Augen und enormes Aufschwellen der Ohren eintrat... dass die Versuchsthiere diesen Eingriff zunächst überstanden, dass aber, unter fortwährender profuser Eiterung, nach einigen Wochen die Ohrender selben nekrotisch vollständig abfielen.

> [Since the vapors of the chloride showed similar derogatory activities to the persons who were engaged with the experiments just described, these experiments had to be stopped.
> It seems, that the chloride at least predominantly develops its violent irritating effects only after its intake into the blood.
> ... that the rabbits after a short period of inhalation of the chloride vapors always died of pneumonia and that, furthermore, a violent inflammation of the ears and the eyes and an enormous swelling of the ears occurred after painting the ears with a trace of the oil... that the test animals got over this operation in the beginning, that however several weeks later, under continous profuse festering, their ears necrotically fell off completely.]

Meyer's theoretically orientated, purely scientific question whether it would be possible to synthesise a homologue of thiophene in this case unleashed a development of greatest political and military moment!

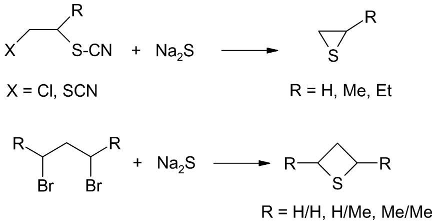
Meyer's student Krekeler (*67*), by the way, really obtained a derivative of the sought-for "homolog" of thiophene, 3-methyl-4*H*-thiopyrane (*β-methylpenthiophen*), by reaction of disodium 2-methylglutarate with phosphorus trisulfide (Equation (17)).



(17)

Methionine [2-amino-4-(methylsulfanyl)butanoic acid, $MeS-CH_2-CH_2-CH(NH_2)-CO_2H$] as an essential proteinogenic amino acid represents the most important naturally occurring thioether. It was, however, only discovered at the beginning of the twentieth century. Mueller (*69*) found it in 1923 as a constituent of caseinogen and egg albumine. Its constitution was proved in 1928 by Barger and Coyne (*70*) who also synthesized racemic methionine by a Strecker synthesis. In agreement with Mueller, they coined the name of the amino acid with respect to its characteristic groups ("*me*thyl*thio*methylala*nine*"). Only in 1931 enantiomerically pure L-methionine was prepared (*71*).

Thiiranes and thietanes. The small-ring cyclic thioethers, thiirane and thietane, were only discovered in the twentieth century. Delépine obtained the former from 2-chloroethyl thiocyanate (*72*) or better from 1,2-bis(thiocyanato)ethane (*73*), and sodium sulfide, which latter method also led to the corresponding alkyl derivatives according to Scheme 3. Tetraarylthiiranes were already mentioned in 1916 (*74*) and described more detailed in 1920 (*75*) by Staudinger and co-workers. The reaction of 1,3-dibromopropanes with sodium sulfide, on the other hand, gave thietanes (Scheme 3) (*76*).



Scheme 3.

Thiophene formally represents a thioether, although the chemical and physical properties of this hetarene are more or less untypical of the class of thioethers. It was discovered in 1882 (*77*) or 1883 (*78*), respectively, by Meyer. He observed the characteristic blue color after the reaction with isatine (“indophenine-test”), which until then had been taken as a special test for benzene (!). Traces (<0.5%) of thiophene had been hidden as an unknown impurity in the so-called purest benzene from bituminous coal tar [Ger.: *reinstem Benzol aus Steinkohlentheer*]. Meyer (*79*) also independently prepared a small amount of an oil which completely agreed with thiophene in all its reactions by passing ethene or acetylene through boiling sulfur. Benzene which had been prepared by decarboxylation of benzoic acid did, of course, not show the indophenine color test (*77*). In his second publication (*78*), he wrote that:

> Bei der Beschreibung des neuen Körpers und seiner Derivate angelangt, erscheint es wünschenswerth, eine passende Nomenclatur einzuführen. Ich will vorausschicken, dass die neue Verbindung die Formel C_4H_4S besitzt, und dass ihre wesentlichste Eigenthümlichkeit die grosse Aehnlichkeit ist, welche sie selbst mit dem Benzol, welche zumal aber ihre Abkömmlinge mit den entsprechenden Benzolderivaten haben. . .
> . . . und auch eine ähnliche Constitution besitzen, nur dass sie, statt vom Benzol, von einem schwefelhaltigen Stammkörper mit 4 Schwefelatomen.
> Für diesen letzteren möchte der Name Thiophen passend sein, welches einerseits den Schwefelgehalt der Substanz, andererseits die grosse Aehnlichkeit derselben und ihrer Derivate mit den Phenylverbindungen, zum Ausdrucke liegt. . .
>
> [Having arrived at the description of the new body and its derivatives, it seems desirable to introduce a suitable nomenclature. I want to mention before that the novel compound exhibits the formula C_4H_4S and, that the striking similarity which this compound itself exhibits to benzene and which, in particular, its derivatives exhibit to the corresponding benzene derivatives represents its most characteristic feature. . . and, furthermore, exhibit a similar constitution but that they are derived from a sulfur containing parent compound with 4 carbon atoms instead of the benzene. . . The name thiophene might be suitable which, on the one hand, expresses the sulfur content of the compound and, on the other hand, the striking similarity of it and of its derivatives with the phenyl compounds. . .]

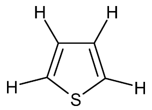
Consequently, he already made the correct structural proposal and assigned a Kekulé-type formula to the compound (*78*):

> Es wäre selbstverständlich verfrüht, die Frage nach der Constitutiondes Thiophens schon jetzt beantworten zu wollen; immerhin möge dieselbe heut wenigstens kurz berührt werden. Zwei Gesichtspunkte verdienen dabei wohl in erster Linie Berücksichtigung: einerseits die Analogie der Formeln des Thiophens und Furfurans:
>
> | Thiophen | Furfuran |
> |---|---|
> | C_4H_4S | C_4H_4O |
>
> vor allem aber andererseits die auffallende Aehnlichkeit, welche das Thiophen, zumal in seinen Derivaten, mit den Verbindungen der Benzolreihe zeigt. Diese letztere Erscheinung wird Jedem, der mit dem Körper und seinen Abkömmlingen zu thun hat, in frappanter Weise entgegentreten. . .
> [It would, of course, be premature to answer the question of the constitution of thiophene right now. Nevertheless, it might today be referred to briefly. Two aspects deserve consideration in the first place: First the analogy of the

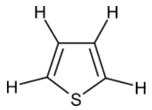
> formulae of thiophene and furan (“furfurane”):
>
> | Thiophene | Furfuran |
> |---|---|
> | C_4H_4S | C_4H_4O |
>
> and, in particular, the remarkable similarity with the compounds of the benzene series which thiophene and especially its derivatives exhibit. This latter phenomenon will strikingly meet everybody who has to do with the compound and its derivatives. . . .]

Correctly, Meyer regarded isomeric thioketone or thioaldehyde-type structures to be out of question. He wrote (*78*):

> . . . so wird man eine vorläufige Formulirung des Thiophens als

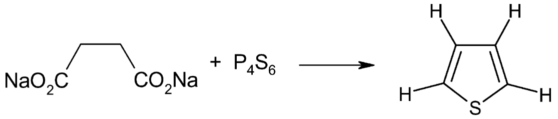


> wenigstens für discutirbar and näherer Prüfung werth erachten. . .
>
> [thus a preliminary formulation of thiophene as



> should at least be worth a discussion and a more detailed examination. . .]

A couple of years later, Meyer (*80*) as well as other authors summarized chemical reactions in which thiophene is formed. A really productive (50% yield) method of preparation from sodium succinate and phosphorus trisulfide (Equation (18)) was found subsequently by Volhard and Erdmann (*81*). This has remained today’s current laboratory method for the synthesis of thiophene (*82*).



(18)

Organic disulfides (disulfanes) are very stable compounds in contrast to the labile oxygen analogs, the peroxides. Therefore, they have been well known for a long time. Certain unsaturated disulfides occur in natural products and particularly in food products and these exhibit remarkable pharmacological properties.

Dimethyl disulfide has been found, strangely enough, in cavities of milky white quartz crystals from Norway. It was detected there by Sjögren in 1906 (*83*) and had probably been formed by decomposition of palaeozoic bacteria.

Diethyl disulfide has been discovered very early. It is identical with Zeise’s above-mentioned *Thialöl* and has been more clearly characterized by Morin (*84*) and by Cahours (*85*). Kekulé and Linnemann (*86*) described a suitable method for its preparation by oxidation of sodium ethanethiolate with iodine (Equation (19)).

$$2\,\mathrm{Et{-}SNa} + \mathrm{I_2} \longrightarrow \mathrm{Et{-}S{-}S{-}Et} + 2\,\mathrm{NaI} \qquad (19)$$

Diallyl disulfide is a natural product that was discovered as a constituent of garlic by Wertheim as early as 1844. He wrote (*30*):

> Bekanntermaßen ist der Knoblauch ein beliebtes Genussmittel des gemeinen Mannes in manchen Ländern; namentlich wird er in Böhmen, Polen und Ungarn in großer Quantität angebaut und consumiert. Er verdankt diese Anwendung hauptsächlich der Gegenwart eines schwefelhaltigen, flüchtigen Körpers, des sogenannten Knoblauchöls.

> [As everybody knows garlic is a favorite luxury food of the man in the street in many a country. Especially in Bohemia, Poland and Hungary it is grown and consumed in large quantities. This usage is owing mainly to the presence of a sulfur containing volatile body, the so-called garlic oil.]

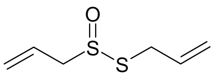
and identified this oil as diallyl disulfide. A more detailed study was performed later on by Semmler (*87*) who wrote:

> . . . dieser bekannte Forscher (Wertheim) hat in dem ätherischen Öle des Knoblauchs ein neues Radikal C_3H_5 aufgefunden und Allyl genannt. . .

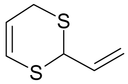
> [. . . this well known researcher (Wertheim) has discovered a novel radical C_3H_5 in the ethereal oil of garlic and has called it allyl. . .]

Thus, the allyl residue which is, now as before, particularly important in modern mechanistic and synthetic organic chemistry, originates from nineteenth-century organosulfur chemistry – as the name as well as the structural moiety. Semmler (*87*) isolated 60% diallyl disulfide and 20% diallyl trisulfide by fractionated vacuum distillation of 800 g of garlic oil which he had obtained from 900 kg (!) of garlic onions (*Allium sativum* L.). Also a minor amount of diallyl tetrasulfide was found but not the simple thioether diallyl sulfide. The diallyl disulfide exists in garlic as its sulfoxide allicin. Semmler also identified disulfides, mainly dipropyl disulfide, and oligosulfides in onions (*Allium cepa* L.) (*88*).

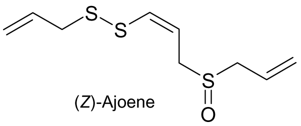
A century later, Block comprehensively attended to the constituents of onions and garlic. He isolated and identified a great number of further sulfur containing constituents using modern analytical methods. Most of these were allylsulfanyl derivatives; some of them were sulfoxides (*89*). For example, 2-vinyl-4*H*-1,3-dithiine and ajoene (Span.: *Ajo* = garlic) may be mentioned. These compounds prevent the aggregation of the thrombocytes and represent, therefore, efficient agents against thrombosis and arteriosclerosis. They could well be the crucial constituents that cause the general healthful and life-prolonging activity, which one – quite correctly – ascribes to the consumption of garlic.



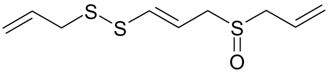
Allicine



2-Vinyl-4*H*-1,3-dithiine



(*Z*)-Ajoene



(*E*)-Ajoene

Cystine has already been mentioned as a highly important naturally occurring disulfide which is connected with cysteine in a redox interrelation. L-Cystine was discovered as early as 1810 by Wollaston (*90*), interestingly not in a peptide but in urinary calculi from which its name was derived (Greek: *kystis* = bladder). In the beginning, its sulfur content was not recognized. The wrong stoichiometric formula $C_6H_{12}N_2O_8$ was derived from an insufficient elemental analysis. As a consequence of the "high oxygen content", the compound was named Cystic Oxyd (*91*). Only in 1838, Thaulow determined the correct formula $C_6H_{12}N_2O_4S_2$ and wondered at the fact that cystine was one of the "few" compounds, which contained five different elements. He had received a small amount of the "rare" and valuable substance from Liebig, who had assumed the compound to contain sulfur (*53*). Cystine is always found in considerable amounts in the urine as well as in urinary and bladder calculi of patients suffering from cystinuria (*92*). No "structure" could, of course, be assigned to the compound at that time. The structures of cystine and cysteine were successfully investigated and disclosed by Baumann (*44*, *45*), Neuberg (*47*), Friedmann (*48*), and Erlenmeyer (*49*) (see above).

Organic oligosulfides ($Ar{-}S_n{-}Ar$) were first described by Otto (*93*). In the same year, Klason reported on the preparation of diethyl, diphenyl, and ditolyl tetrasulfide. Dimethyl tetrasulfide turned out to be unstable: it was transformed into the more persistent dimethyl trisulfide by extrusion of sulfur (*94*).

5. Sulfonium compounds

Sulfur, as an element of the third period of the periodic table, is much more nucleophilic when compared with oxygen. Therefore, it readily reacts with electrophiles under formation of stable compounds with coordination numbers higher than two at the sulfur. Furthermore, the possibility of an octet expansion with participation of low-energy 3d orbitals may play a role, *e.g.* for the *S*-oxidized sulfur compounds to be discussesd in Section 10. For this reason, interesting types of sulfur compounds exist where the corresponding oxygen analogs are unknown.

Thus, sulfonium salts are much more stable when compared with the corresponding oxonium salts. They are formed by alkylation of the organic sulfides and are the analogs of the quaternary ammonium salts. In 1864, von Oefele (*95*) obtained triethylsulfonium iodide by alkylation of diethyl sulfide with iodoethane. He also described the free base triethylsulfonium hydroxide which was formed by interconversion of the iodide with silver oxide (Equation (20)) and which turned out to exhibit very strong alkaline properties. Within the next three years, Cahours (*96*), Dehn (*97*), and Saytzeff (*98*) published papers on trialkylsulfonium salts and hydroxides including the trimethylsulfonium derivatives.

$$\mathrm{Et{-}S{-}Et} + \mathrm{Et{-}I} \longrightarrow [\mathrm{Et_3S}]^+\ \mathrm{I}^- \xrightarrow{\mathrm{Ag_2O}} [\mathrm{Et_3S}]^+\ \mathrm{OH}^- + \mathrm{AgI} \qquad (20)$$

Sulfonium cations exhibit a pyramidal structure since the barrier of inversion is high in contrast to that of the tertiary amines. They are therefore chiral if three different substituents are attached to the sulfur. The fourth corner of the tetrahedron is occupied by the lone pair electrons. The expected enantiomers could be separated by Smiles as early as 1900 (*99*). He prepared ethylmethylphenacylsulfonium bromide from ethyl methyl sulfide and phenacyl bromide. This racemic salt was converted into the two diastereoisomeric *d*-bromocamphoresulfonates $[l\text{-}R_3S^+][d\text{-}BCS^-]$ and $[d\text{-}R_3S^+][d\text{-}BCS^-]$, which could be separated by fractionated crystallization from ethanol. Finally, the two enantiomeric picrates $[l\text{-}R_3S^+][C_6H_2N_3O_7^-]$, $[\alpha]_D = -9.2°$ and $[d\text{-}R_3S^+][C_6H_2N_3O_7^-]$, $[\alpha]_D = +8.1°$, were isolated.

6. Thiocarbonyl compounds

Only in the twentieth century, simple thioaldehydes and aliphatic thioketones could be obtained in a pure state. They are extremely sensitive compounds. Because of the large radius of the sulfur atom, the $p\pi$–$p\pi$ overlap between carbon and sulfur is significantly weaker as with oxygen. The tendency to form double bonds is, therefore, less pronounced. The simple thiocarbonyl compounds hence easily trimerize to 1,3,5-trithianes or tautomerize to enethiols under removal of the carbon–sulfur double bond. They are, furthermore, easily oxidized to the corresponding carbonyl compounds.

Diarylthioketones are the most persistent compounds of the series because they cannot form enethiols and, due to the bulkiness of the aryl substituents, their tendency to trimerize is not that pronounced.

4,4′-Bis(dimethylamino)thiobenzophenone ($Me_2N{-}C_6H_4{-}CS{-}C_6H_4{-}NMe_2$), the analog of Michler's ketone, is the longest known derivative. As a phenylogous thiourea, it is stabilized by mesomerism. Kern (*100*) obtained it [*stahlblauglänzende, in durchfallendem Lichte rothgefärbte, spiessige Krystalle* (steel-blue gleaming, pike-shaped crystals appearing red-colored in light falling through)] in 1886 by treatment of *N,N*-dimethylaniline with thiophosgene. It was also produced industrially (*101*) from Michler's ketone (*102*) and phosphorus pentasulfide (*103–105*) or from the related imine ("auramine") (*106*) with the goal to produce triphenylmethane dyes. In 1887, it was studied systematically by Baither (*107*) who had obtained a larger amount of the thioketone from the Kern and Sandoz company. In the introduction of his paper, he stated:

> Theoretisches Interesse erregt er besonders durch seine Natur als » Thioketon « — also als Vertreter einer Körperklasse, über die zur Zeit sehr wenig bekannt ist, und die bisher meist nur in Form polymerer »Duplo–Thioketone « zu bestehen schien.
>
> [It raises a particular theoretical interest because of its nature as a » thioketone « — *i.e.*, an example of a class of bodies, of which very few is known at the present time and which seemed to exist, until now, only in the form of polymeric » duplo–thioketones«.]

The thioketone surprised by its fascinating coloring (*schön rubinrothe Krystallblätter mit lebhaft blauem Glanze* or *glitzerndes, cantharidengrün schimmerndes Krystallpulver* [beautifully ruby crystal leaves with a vivid blue lustre or glittering cantharide-green glimmering crystal powder]) (*107*). In solution, it displays an almost chameleon-like change of colors. Baither wrote (*107*):

> . . . Das Thioketon löst sich leicht in Chloroform mit dunkelrother Farbe. . . in Eisessig und zwar mit grüner Farbe. Die Schwefelkohlenstofflösung ist im reflektirten Lichte prachtvoll grasgrün, im durchfallenden dunkelroth. . . in Salzsäure. . . mit sehr viel Wasser eine schöne, tiefgrüne Lösung. . .
>
> [. . . The thioketone easily dissolves in chloroform with a deep red color. . . in glacial acetic acid with a green color. The solution in carbon disulfide is magnificently grass-green in the reflected light, dark red in the through falling light. . . in hydrochloric acid. . . with plenty of water a beautiful, deep green solution. . .]

But he also pointed out:

> Die schöne Färbung ist dem Keton eigen und rührt nicht von fremden Beimengungen her. . .
>
> [The beautiful color is a property of the thioketone itself and does not originate from extraneous ingredients. . .]

The contemporaries were so irritated about this chameleon-like coloring that they did not accept the simple structure of the thioketone. Meyer, for instance, wrote in a footnote to Baither's paper (*107*):

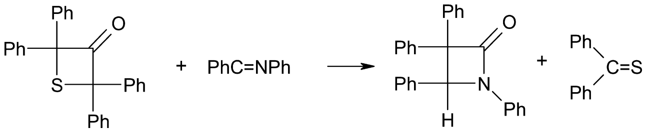
> Hiernach ist es kaum wahrscheinlich, dass der Körper ein einfaches Keton ist; da Michler's $CO[C_6H_4N(CH_3)_2]_2$ und auch Engler's $CS(C_6H_5)_2$ farblos (sic!) sind, so ist die intensive Färbung der Substanz bei Annahme der Keton-Formel nicht verständlich. Vielmehr sind tautomere Formen (C. Laar –; P. Jakobson bezeichnet die Erscheinung der Tautomerie zutreffender als »Desmotropie«) wahrscheinlich. . .
>
> [Therefore, it is hardly probable that the body should be a simple ketone. Because Michler's $CO[C_6H_4N(CH_3)_2]_2$ as well as Engler's $CS(C_6H_5)_2$ are colorless (sic!) the intense coloring of the substance is not reasonable under the assumption of a ketone formula. Rather, tautomeric formulae (C. Laar –; P. Jakobson, more correctly, call the phenomenon of tautomerism as »desmotropism«) are more probable . . .]

Meyer proposed strange alternative formulae with pentavalent nitrogen. However, shortly after that, Fehrmann (*106*) as well as Graebe (*108*) rejected these formulae. They had obtained the thioketone by the reaction of auramine with carbon disulfide or with hydrogen sulfide and had characterized the new compound once more. In the case of thioketones, the fixation on the hypothesis of an analogy between oxygen and sulfur, which, apart from that, had turned out to be quite successful, obviously prevented the realization that also very significant differences exist between the corresponding compounds. As we nowadays know, the deep coloring of the thiocarbonyl compounds is due to the larger atomic radius of sulfur when compared with oxygen and, as a consequence, a higher polarizability of the C=S double bond (see above), which causes a bathochromic shift of the $n \rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ electron excitation bands into the visible region of the spectrum. Also, the striking solvatochromism is now well understood.

Thiobenzophenone itself, the prototypical diarylthioketone, is much less stable than Michler's thioketone. It could not be prepared until 1919, when Vorländer and Mittag (*109*) isolated it at least in a nearly pure form (*annähernd reines Thiobenzophenon* (*110*)) (Equation (21)) because it cannot be separated from its easily formed autoxidation product benzophenone. Earlier reports on its preparation have all turned out to be incorrect. For instance, Engler's "thiobenzophenone" (*111*), which Meyer had regarded as indicative of a wrong structure of Michler's thioketone (*107*), was a colorless compound and thus surely was not thiobenzophenone. According to Staudinger (*110*), it consisted mainly of dibenzhydryl disulfide. Also Gattermann's light-blue reaction product of benzophenone dichloride with potassium sulfide (*112*) contained at least 50% benzophenone (*110*), whereas diaryl thioketones with electron-donating substituents such as OR or NR_2 in the *para*-position were easily available as deeply colored (*... die Farbe als dem Körper in Wirklichkeit zukommend... dass die Gruppe .CS. zu den chromophoren gehört* [... the color is really due to the bodies... that the .CS. group belongs to the chromophorus ones] (*113*)) compounds according to Equation (22) (*113*). Finally, Staudinger and Schönberg's investigations were successful. Independently, they described three suitable methods (Equation (23) (*110*), Equation (24) (*114*), and Equation (25) (*115*)), for the preparation of analytically pure thiobenzophenone, beautiful deep-blue colored crystals with m.p. 51–52 °C (*103–105*).

$$Cl_3C{-}S{-}Cl + C_6H_6 + AlCl_3 \longrightarrow Ph{-}CS{-}Ph \qquad (21)$$

$$2ArH + CSCl_2 + AlCl_3 \longrightarrow Ar{-}CS{-}Ar \qquad (22)$$



(23)

$$Ph{-}CO{-}Ph + H_2S + HCl \longrightarrow Ph{-}CS{-}Ph \qquad (24)$$

$$Ph_2CCl_2 + CH_3{-}CO{-}SH \longrightarrow Ph{-}CS{-}Ph \qquad (25)$$

Aliphatic thioketones are even more labile than the aromatic derivatives. They could only be prepared and unambigously characterized in the twentieth century. Earlier attempts had only raised the presumption that thioketones could have formed during certain reactions. Fromm and Baumann, for instance, described a violet coloration and a characteristic obnoxious smell when they treated acetone with hydrogen sulfide in the presence of hydrogen chloride or amines as catalysts. They isolated, however, only the cyclic trimer of thioacetone (2,2,4,4,6,6-hexamethyl-1,3,5-trithiane) as the product (*116*). The stench of the aliphatic thioketones is really completely intolerable. Fromm and Baumann had to break off their investigations when the citizens of Freiburg protested against the pollution of whole quarters of Freiburg. In Part II of their publication (*117*), the authors wrote:

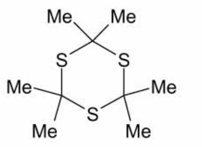
> Als... das... Reactionsproduct von 100g Aceton concentrierter Salzsäure und Schwefelwasserstoff bei sorgfältiger Kühlung mit Wasserdampf destillirt wurde, verbreitete sich der Geruch in kurzer Zeit bis auf Entfernungen von 3/4 Kilometer bis in weit abgelegene Stadttheile. Bewohner der dem Laboratorium benachbarten Strassen beschwerten sich darüber, dass die riechende Substanz bei manchen Personen Ohnmachtsanfälle, Uebelkeit und Erbrechen bewirkt hätte. Als ein anderes Mal eine Quantität von 30 g des schon einmal destillirten Rohproductes im Vaccum destillirt wurden, geriethen die Bewohner der angrenzenden Strassen in dieselbe Aufregung wie im ersterwähnten Falle. Bei beiden Destillationen fand ein merkbarer Verlust an Substanz durch Verflüchtigung nicht statt. Aeusserst geringe Mengen des schwefelhaltigen Körpers genügten also, um Millionen von Kubikmetern Luft zu verpesten. Hierbei verdient bemerkt zu werden, dass der Geruch im Laboratorium nicht belästigender war, als wenn man mit bekannten Sulfiden und Mercaptanen arbeitet. Wir selbst haben an uns keine gesundheitsschädlichen Wirkungen desselben beobachtet. Da indessen jedes Experiment mit der fraglichen Substanz einen Sturm von Klagen gegen das Laboratorium entfesselte, haben wir die Versuche, das Thioaceton selbst zu gewinnen, schon vor längerer Zeit aufgegeben.

> [When... the... product of the reaction of 100 g of acetone concentrated hydrochloric acid and hydrogen sulfide was steam-distilled under careful cooling the smell spread over distances of 3/4 of kilometers into remote city districts

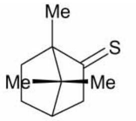
> in a short time. The inhabitants of the streets in the neighborhood of the laboratory complained about seizures of unconsciousness, nausea and vomiting. When, in another case, a quantity of 30 g of the crude product, which had already been distilled, was distilled in a vacuum, the inhabitants of the neighboring streets grew alarmed in the same way as the above mentioned people. During both the distillations a significant loss of the substance by evaporation did not occur. Obviously, extremely tiny amounts of the sulfur containing body were sufficient to raise a stench in millions of cubic meters of air. Here, one should annotate that the smell in the laboratory did not harass more as if one works with known sulfides or mercaptans. We ourselves did not recognize any noxious effects of it. Since, however, every experiment with the substance in question raised public outcries against the laboratory, we gave up our efforts to isolate pure thioacetone some time ago.]

These circumstances surely represent one of the reasons why the chemistry of thioketones could not be further studied for a long time.

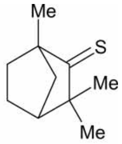
In the 1930s, finally, pure thiocamphor (*118*) and thiofenchone (*119*) were prepared as the first two examples. They are particularly stabilized on account of their special, highly branched bicyclic structure. In addition, their smell keeps within reasonable limits.



Hexamethyl-1,3,5-trithiane



Thiocamphor



Thiofenchone

Finally, in 1963, Mayer and Berthold (*120*) obtained the simplest aliphatic thioketone, thioacetone, as well as a large number of other thioketones as pure and well-defined monomers through cleavage of ketals and enolethers with hydrogen sulfide in the presence of acidic catalysts. They likewise wrote, however, about thioacetone: . . . *der Geruch dieses instabilen roten Öles ist tatsächlich kaum zu beschreiben* . . . [. . . the odor of this unstable red oil is really almost past all description. . .] (*103, 105*).

Thioaldehydes have even longer escaped any attempted synthesis and unequivocal characterization. The first aromatic example, 2,4,6-tri-*tert*-butylthiobenzaldehyde, was prepared in 1982 by Okazaki *et al.* in Japan (*121*). A chloroform solution containing 50% of the aliphatic thiopivalic aldehyde $(CH_3)_3C{-}CH{=}S$ was obtained in 1983 by Vedejs and Perry (*122*).

7. Thiocarboxylic acids and their derivatives

Thioacetic acid (ethanethioic acid) was first prepared in 1854 by Kekulé who obtained it by thionation of acetic acid with phosphorus penta- or trisulfide according to Equation (26) (*17*).

$$CH_3{-}CO{-}OH + P_4S_{10}(P_4S_6) \longrightarrow CH_3{-}CO{-}SH \qquad (26)$$

Kekulé furthermore described salts of thioacetic acid, *S*-ethyl thioacetate (*c.f.* however, Michler (*123*)), and thioacetic anhydride (diacetyl sulfide), which he also obtained by thionation reactions. Kekulé performed these studied particularly under the aspect of the “theory of types”. He wrote in his *Notiz über eine neue Reihe schwefelhaltiger organischer Säuren* [note on a new series of sulfur containing organic acids] (*17*):

> Wenn man die Verbindungen der anorganischen und der organischen Chemie nach Reihen ordnet, deren Typen den einfachsten Verbindungen der anorganischen Chemie entnommen sind, so sieht man leicht, daß auch in der organischen Chemie die Reihe von Verbindungen, deren Typus der Schwefelwasserstoff [H_2S] ist, vollständig der Reihe des Wassers gleichlaufen müsse. Außer den Mercaptanen und neutralen Schwefelwasserstoffäthern, die den Alkoholen und Aethern der Wasserreihe entsprechen, müssen demnach auch die den Säuren, wasserfreien Säuren und Säureethern entsprechenden Gruppen der Schwefelwasserstoffreihe erhalten werden können.
> Dieß veranlasste, eine Reaction aufzusuchen, welche gestatten würde, durch Einführen von Schwefel an die Stelle des Sauerstoffs die Glieder der Wasserreihe in die der Schwefelwasserstoffreihe umzuwandeln.

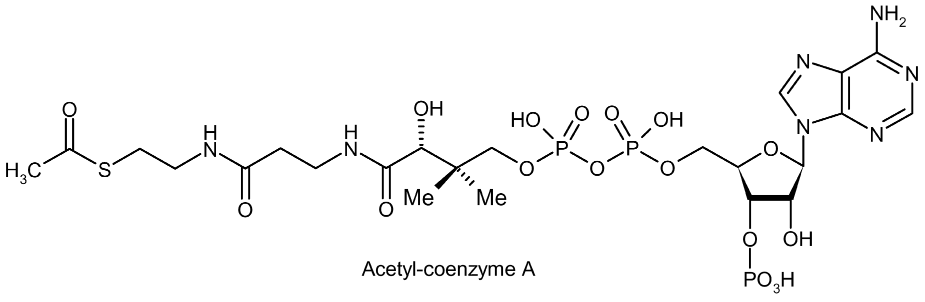
> Eine solche Reaction zeigen die Schwefelverbindungen des Phosphors, das Phosphortersulphid (P_2S_3) und das Phosphorpentasulfid (P_2S_5)...
>
> Durch Einwirkung von Wasser auf die Sulphide des Phosphors entsteht Schwefelwasserstoff und eine Säure des Phosphors ...
>
> Dieselbe Reaction zeigen die organischen, in die Reihe des Wassers gehörigen Verbindungen. Aus Alkohol wird durch Drei- oder Fünffach-Schwefelphosphor mit Leichtigkeit Mercaptan erhalten; während aus Aether durch dieselben Verbindungen Schwefeläthyl erzeugt wird...
>
> Aus einem Glied der Wasserreihe, das als Wasser angesehen werden kann, in welchem 1 Atom Wasserstoff durch ein Radical vertreten ist, erhält man ein entsprechendes Glied der Schwefelwasserstoffreihe; während durch eine organische Verbindung, die als Wasser betrachtet werden kann, in welchem die beiden Atome Wasserstoff durch Radicale ersetzt sind, ein Schwefelwasserstoff erzeugt wird, der an der Stelle von 2 At. Wasserstoff zwei Atome eines Radicals enthält.
>
> Daß die Säuren, die wasserfreien Säuren und die Säureäther dasselbe Verhalten zeigen würden, konnte kaum bezweifelt werden; der Versuch hat es in der That bestätigt...

> [If one arranges the compounds of inorganic and organic chemistry in series, which are taken from the simplest compounds of inorganic chemistry, one will easily recognize that also in organic chemistry the series of compounds, the type of which is hydrogen sulfide [H_2S], must parallel the series of water. Besides the mercaptans and the neutral ethers of hydrogen sulfide, which correspond with the alcohols and ethers, also the groups of the hydrogen sulfide series, which correspond with the acids, anhydrous acids and acid ethers must be obtainable.
>
> This prompted us to look for a reaction which would allow one to change the members of the water series into those of the hydrogen sulfide series by introducing sulfur into the position of oxygen.
>
> Sulfur compounds of phosphorus like phosphorus trisulfide (P_2S_3) and phosphorus pentasulfide (P_2S_5) exhibit such a reaction...
>
> By the reaction of water on the sulfides of phosphorus, hydrogen sulfide and an acid of phosphorus are formed...
>
> Organic compounds belonging to the water series show the same reaction. Mercaptan is obtained with ease from alcohol and triple or pentuple sulphuric phosphorus, whereas sulphuric ethyl is formed from ether by the same reagents...
>
> One obtains a member of the hydrogen sulfide series from a corresponding member of the water series, which may be considered as water in which 1 atom of hydrogen is substituted by a radical; whereas a hydrogen sulfide which contains two atoms of a radical instead of 2 at. of hydrogen is generated from an organic compound which can be considered as water in which both the two atoms of hydrogen are replaced by radicals.
>
> One could hardly doubt that the acids, anhydrous acids and acid ethers would exhibit the same behavior; the experiment has really confirmed this...]

Kekulé thus, within the framework of the theory of types, classes the thiocarboxylic acids and their derivatives with the “hydrogen sulfide type” in analogy to the corresponding oxygen compounds which belong to the “water type”. His publication represents another example of the importance of typical organosulfur compounds for the understanding of the constitution of organic compounds in general. This idea also very well agreed with the observation that potassium thioacetate gave diacetyl disulfide on reaction with iodine – in perfect analogy with the reaction of ethanethiol (see Equation (19)) (*86*).

Several years later, potassium thioacetate was also obtained by thiolysis of acetyl chloride (*124*) or phenyl acetate (*125*) with potassium hydrogen sulfide.

Acetyl-coenzyme A (Acetyl-CoA), the activated thioacetic acid *S*-ester in which the acetic acid is connected with pantothenic acid *via* the SH group of a cysteamine residue, was discovered in 1951 by Lynen *et al.* (*126*) and plays of course a fundamental role in the metabolism of carbohydrates and lipoids and in the biosynthesis of polyketides.



Acetyl-coenzyme A

Possibly, *S*-methyl thioacetate represents a key intermediate for the generation of living matter. It can be taken as a simpler precursor of acetyl-CoA, which, in an early state of the evolution, could have played the role of the latter during the generation of organic molecules. Huber and Wächtershäuser have shown that methanethiol can be formed by the reaction of carbon monoxide and carbon dioxide with iron sulfide and hydrogen sulfide, the compounds which are all present in the deep sea. On the other hand, methanethiol and carbon monoxide react in aqueous solution at 100°C (in fumaroles in the deep sea) under C−C coupling and formation of acetic acid and also in a parallel reaction directly to *S*-methyl thioacetate according to Equations (27) and (28) (*127*).

$$CH_3{-}SH + CO + H_2O \xrightarrow{NiS/FeS} CH_3{-}COOH + H_2S \tag{27}$$

$$2CH_3{-}SH + CO \xrightarrow{NiS/FeS} CH_3{-}CO{-}SCH_3 + H_2S \tag{28}$$

Accordingly, thiocarboxylic esters are by no means insignificant, exotic species but compounds with a remarkable importance for the life sciences.

S-ethyl thioacetate was first obtained by Michler (*123*) who prepared it by alkylation of thioacetic acid, which exclusively leads to this isomer, as well as from ethanethiol and acetyl chloride. Analogously, he prepared *S*-phenyl thioacetate and *S*-phenyl thiobenzoate from thiophenol. He could, however, not confirm Kekulé's (*17*) description of the preparation of *S*-ethyl thioacetate by sulfuration of ethyl acetate with phosphorus pentasulfide. In 1903, Weigert (*128*) found a new general method for the preparation of aliphatic and aromatic thiocarboxylic acid derivatives by reaction of carbonyl sulfide COS with Grignard reagents.

O-ethyl thioacetate and its homologs, on the other hand, could be only prepared in 1909 by thiolysis of *O*-ethyl imidates according to Equation (24) (*129*), when it became apparent that these other isomers should also exist. Their structure was obvious as they are transformed into thioamides by ammonia (Equation (29)) (*129*). Thionocarboxylic acid *O*-esters (*103*, *130*) are rather labile compounds due to their thiocarbonyl group.

$$\begin{aligned} &R{-}C({=}NH_2^+){-}OEt + H_2S \longrightarrow R{-}CS{-}OEt \longrightarrow R{-}CS{-}NH_2 \\ &R = Me, Et, Ph \end{aligned} \tag{29}$$

Thiobenzoic acid (m.p. 24 °C) was prepared by Engelhardt, *et al.* (*131*) according to Equation (30) through thiolysis of *S*-ethyl thiobenzoate, which they had obtained from benzoyl chloride and ethanethiol. This ester had already been prepared from lead or sodium ethanethiolate and benzoyl chloride in 1863 by Tjuttschew (*132*).

$$C_6H_5{-}CO{-}SEt + KSH \longrightarrow C_6H_5{-}CO{-}S^-K^+ \xrightarrow{HCl} C_6H_5{-}CO{-}SH \tag{30}$$

Engelhardt *et al.* (*131*) identified a substance (m.p. 120 °C) as dibenzoyl disulfide (m.p. 128 °C) which Cloëz (*133*) had obtained and taken for thiobenzoic acid:

> Die... Säure C^7H^6 SO erwies sich als ganz verschieden von der Cloëzschen Thiobenzoesäure
>
> [The... acid C^7H^6 SO turned out to be quite different from Cloëz's thiobenzoic acid]

They also prepared *S*-amyl thiobenzoate, dibenzoyl sulfide, the above-mentioned dibenzoyl disulfide, as well as *S*-ethyl thiocinnamate Ph−CH=CH−CO−SEt. According to Schiller and Otto (*134*), also *S*-phenyl thiobenzoate $C_6H_5{-}CO{-}SPh$ (m.p. 56 °C) can be easily prepared from benzoyl chloride and thiophenol as one would expect – in contrast to the publication of Michler (*123*) who had claimed diphenyl disulfide (m.p. 60 °C) to be the only product of this reaction – obviously an analytical mistake, in Schiller and Otto's opinion.

Dithiocarboxylic acids and their derivatives, to a certain extent, are delicate compounds. They were not easy to achieve with the nineteenth century's preparative methods. Last but not the least, they generate heavy, not to say prohibitive, inconveniences on account of their offensive odor as Houben (*135*) pointed out in his paper on the preparation of dithioacetic acid:

> Ein intensiver, die Verschlüsse durchdringender Geruch macht sich schon zu Beginn der Umsetzung bemerkbar und vermag, selbst in weiteren Entfernungen den Aufenthalt zu einem unerträglichen zu gestalten. Gut wirkende Abzüge und sonstige Vorsichtsmaßregeln versagen anscheinend dem entsetzlichen Geruch der Methylcarbithiosäure gegenüber vollständig, und das Arbeiten mit der Substanz stellt an die Geduld des Experimentators außergewöhnliche Anforderungen.
>
> [An intense odor penetrating the seals makes itself felt from the beginning of the reaction and has the power to turn ones presence to an unbearable one even over long distances. Well operating hoods and other precautionary measures obviously fail completely in the face of the horrible odor of the methylcarbithioc acid. Working with the substance makes extraordinary demands on the patience of the experimentator.]

Therefore, one is not astonished that syntheses were described only relatively late. Moreover, some early reports turned out not to hold good. A real breakthrough in the field of dithiocarboxylic acids and their esters was only achieved at the beginning of the twentieth century, mainly by Houben. In his first relevant publication on this topic, he presented a valuable historical summary on the experimental efforts which had been undertaken in the nineteenth century in order to prepare these problematic compounds. In the following, his text will be given word-by-word. After an introductory treatment of the related dithiocarbonates (xanthates and dithiocarbamates) and trithiocarbonates, he wrote (*136*). (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission):

> Während sich aber die .CS.SH-Gruppe leicht mit Sauerstoff oder Stickstoff verknüpfen liess, ist von Alkyldithiosäuren, in welchen also die genannte Gruppe mit Kohlenstoff kernsynthetisch verbunden ist, sehr wenig bekannt, und nur in der aromatischen Reihe, bei der Dithiobenzoësäure, liegen einige Beobachtungen vor, die sich aber nur auf eine analytische Angabe zu stützen vermögen. Genauer untersucht sind einige Dithiolactone, also innere Ester von Oxy-dithiosäuren, so das von Gabriel und Leupold[10] (*137*) aus o-Cyanbenzylchlorid und Kaliumsulfhydrat gewonnene Dithiophthalid und das Diphenyldithiophthalid[1] (*138*).
>
> Fleischer[2] (*139*) ist der erste, der in seinem »Disulfobenzol« geringe Mengen einer wirklichen Dithiosäure, der Dithiobenzoësäure, in Händen hatte. Er gewann sie durch Erwärmen von Benzalchlorid mit alkoholischem Kaliumsulfhydrat (wahrscheinlich in Folge von Verunreinigung des Letzteren mit Kaliumdisulfid) und nachheriges Fällen mit Wasser, welches, von den ausgefällten Reactionsproducten getrennt, auf Zusatz von Salzsäure ein rothes Oel, das » Disulfobenzol «, ausschied. Die weingeistige Lösung dieses Oels ergab mit Blei-, Silber- und Kupfer-Salzlösungen schwarze, mit Platin- und Gold-Salzen braune, mit Eisensalz weisse, mit Nickelsalz violette und mit Sublimatlösung hellgelbe Fällung. Das Quecksilbersalz krystallisirte aus Benzol in gelben Nädelchen. Die Analyse dieser nur in geringer Menge gewonnenen Verbindung ist die einzige, in der Literatur der Dithiosäuren sich findende, überdies, wie ein Vergleich der von Fleischer gefunden und berechneten Werthe ergibt, ... nicht von zwingender Beweiskraft. Auch die von Fleischer angegebenen Farben der von ihm gefällten Salze zeigen, dass die dargestellten Niederschläge wahrscheinlich mit Schwermetallen verunreinigt gewesen sind, denn das dithiobenzoësaure Blei ist nicht schwarz, sondern roth, das Silbersalz chokoladenbraun; die beiden Eisensalze grün.
>
> Zwei Jahre später als Fleischer erwähnen Engelhardt, Latschinoff und Malyscheff[3] (*131*) in einer kurzen Bemerkung das dithiobenzoësaure Blei, das sie aus Benzoylchlorid and Schwefelblei in kleiner Menge erhalten hatten, und im gleichen Jahr erscheint eine ausführliche Mittheilung von Engelhardt und Latschinoff[4] (*140*) «über Dithiobenzoësäure», welche Bezeichnung hier zuerst auftritt. Die Autoren beschreiben genau Blei-, Silber- und Quecksilber-Salze der Säure, die sie nach einer neuen Methode, aus Benzotrichlorid und Schwefelkalium, darstellten, und die Dithiobenzoësäure selbst als rothviolettes, zersetzliches Oel. Ebenso geben sie schon die Beobachtung an, dass das dithiobenzoësaure Blei nur von starker Mineralsäure zersetzt werde, aus Schwefelkohlenstoff in feinen, orangerothen Nadeln krystallisire, dass das Quecksilbersalz in Aether, Alkohol und Benzol löslich und aus Alkohol in röthlichgoldgelben, dem Musivgold ähnlichen Blättchen zu erhalten sei. Analog gewannen sie aus Chlorbenzotrichlorid und Schwefelalkali die Chlordithiobenzoësäure, deren aus Benzol und Schwefelkohlenstoff in rothen Nadeln krystallisirendes Blei- sowie das Quecksilbersalz, das sich aus alkoholischer Lösung in grün-goldgelben Blättchen abscheiden soll. Trotz all' dieser in's Einzelne gehenden Beobachtungen fehlen aber auch hier die analytischen Daten gänzlich, und es finden sich auch keine sonstigen Constanten, obschon deren Angabe besonders leicht gewesen wäre, da die meisten der dithiosauren Salze Schmelzpunkte besitzen.
>
> Klinger[1] (*141*) stellte 14 Jahre später abermals die Dithiobenzoësäure aus Benzalchlorid und Kaliumsulfhydrat her und erwähnt wieder das aus Xylol krystallisirende Bleisalz, bis endlich in neuerer Zeit C. V. Jörgensen[2] (*142*) über ausgedehnte Versuche zur Gewinnung von Dithiosäuren berichtet. Der letztgenannte Forscher schlug zwei verschiedene Wege ein, um besonders auch zu aliphatischen Dithiosäuren zu gelangen. Einmal übertrug er die Methode von Engelhardt und Latschinoff auf aliphatische Verbindungen, indem er an Stelle des Benzotrichlorids

Methylchloroform mit alkoholischem Schwefelkalium behandelte, und zweitens versuchte er durch Einwirkung von Schwefelkohlenstoff auf Natrium-Zinkmethyl eine Additionsreaction folgender Art auszuführen:

$$CH_3Na + CS_2 = CH_3.CS_2Na.$$

Beide Versuche verliefen nicht in der gewünschten Weise, obschon Jörgensen einmal rothviolette Tropfen eines Oels beobachtete, die möglicher Weise aus Dithiosäure bestanden haben.
Dagegen gaben kurz nach dem Erscheinen der Studie von Jörgensen Houben und Kesselkaul[3] (*143*) in einer kurzen, vorläufigen Notiz an, dass es ihnen gelungen sei, die Alkylmagnesiumhalogenide Grignard's durch Einwirkung von Schwefelkohlenstoff in dithiosaure Salze zu verwandeln, und erbrachten damit den ersten Beweis für die Möglichkeit, auch an die doppelte Bindung zwischen Kohlenstoff und Schwefel Alkylmagnesiumhaloïde ebenso anzulagern, wie an die Kohlenstoff-Sauerstoff-Doppelbindung. Sachs und Lövy[4] (*144*) benutzten dies dann in der Folge zu einer Reihe interessanter Synthesen, in denen sie zeigten dass sich die Alkylmagnesiumhaloïde durch Senföle in die Alkylamide der um ein Kohlenstoffatom reicheren Thionsäuren überführen lassen, während Weigert[5] (*128*) durch Umsetzung der Organomagnesiumverbindungen mit Kohlenoxysulfid eine neue Darstellungsweise der Thiolsäuren lehrte.

[Whereas the .CS.SH group could be easily linked to oxygen or nitrogen only little is known about alkyldithioic acids, in which the respective group is linked core-synthetically to carbon and only a few observations in the aromatic series *i.e.* the dithiobenzoic acid, exist, which are however based on only a single analytical figure. Several dithiolactones *i.e.* internal dithioesters of thiolo-dithiocarboxylic acids, have been investigated more precisely, such as dithiophthalide, which Gabriel and Leupold[10] (*137*) have prepared from o-cyanobenzyl chloride and potassium sulfhydrate as well as diphenyldithiophthalide[1] (*138*). Fleischer[2] (*139*) is the first to keep in hand small amounts of » disulfobenzene«, a real dithioacid, *i.e.* dithiobenzoic acid. He produced it by heating benzal chloride with alcoholic potassium sulfhydrate (probably as a consequence of contamination of the latter with potassium disulfide) and subsequent precipitation with water, which was separated from the solid reaction products and gave a red oil, the » disulfobenzene «, on addition of hydrochloric acid. The alcolic solution of this oil gave black precipitates with lead, silver and copper salt solutions, brown precipitates with platinum and gold salts, a white precipitate with iron salt, a violet precipitate with nickel salt and a light yellow precipitate with mercury salt. The mercury salt crystallised from benzene as yellow needles. The analysis of this compound of which only a small amount could be obtained represents the only one found for dithio acids in the literature. As a comparison of the found and the calculated values shows it is, moreover, . . . not even doubtlessly conclusive. Furthermore, the colors of the precipitated salts given by Fleischer show that the precipitates were probably contaminated with heavy metals since lead dithiobenzoate is not black but red, the silver salt is chocolate brown, both iron salts are green.
Two years after Fleischer's publication, Engelhardt, Latschinoff and Malyscheff[3] (*131*) mention, in a short remark, lead dithiobenzoate, of which they had obtained a small amount from benzoyl chloride and lead sulfide, and a comprehensive publication of Engelhard and Latschinoff[4] (*140*) » on dithiobenzoic acid « appeared in the same year, in which this name is used for the first time. The authors precisely describe the lead, silver and mercury salts, which they had prepared by use of a novel method from benzotrichloride and potassium sulfide as well as the dithiobenzoic acid itself, as a red-violet, decomposing oil. As well, they already mention the observation that lead dithiobenzoate is decomposed only by strong mineral acids, crystallizes from carbon disulfide as tiny orange-red needles, that the mercury salt is soluble in ether, alcohol and benzene and can be obtained from alcohol as reddish-golden-yellow leaflets which resemble mosaic gold. Analogously, they prepared chlorodithiobenzoic acid from chlorobenzotrichloride and alkali sulfide, its lead salt, which crystallizes as red needles from benzene and carbon disulfide, and the mercury salt, which should be deposited as green-golden-yellow leaflets from alcoholic solutions. However, in spite of all these detailed observations any analytical data are again missing nor can other constants be found although their determination should have been particularly easy since most of the dithiobenzoate salts exhibit melting points."
14 years later, Klinger[1] (*141*) once more prepared dithiobenzoic acid from benzal chloride and potassium sulfhydrate and again mentions the lead salt which crystallizes from xylene, until finally and recently C.V. Jörgensen[2] (*142*) reported comprehensive experiments on the preparation of dithioacids. The latter scientist chose two different routes in order to get, in particular, the aliphatic dithioacids. Firstly, he applied Engelhard and Latschinoff's method on aliphatic compounds by reacting alcoholic potassium sulfide on methylchloroform instead of benzotrichloride and, on the other hand, he tried to react carbon disulfide with sodium zinc methyl in order to achieve an addition of the following kind:

$$CH_3Na + CS_2 = CH_3.CS_2Na.$$

Both these experiments failed, although Jörgensen, in a single case, observed red-violet drops of an oil, which possibly could have been a dithioacid.

On the contrary, shortly after the publication of Jörgensen's study Houben and Kesselkaul[3] (*143*) in a short preliminary note reported that they had succeeded in transforming Grignard's alkyl magnesium halides into dithiocarboxylate salts by reaction with carbon disulfide. They thereby provided the first proof for the possibility to add alkyl magnesium halides to the double bond between carbon and sulfur, in the same way as for the carbon-oxygen double bond. In the following time, Sachs und Lövy[4] (*144*) used this in a series of interesting syntheses in which they demonstrated that alkyl magnesium halides can also be transformed into the alkylamides of carboxylic acids with an additional carbon atom by reaction with mustard oils. Furthermore, Weigert[5] (*128*) taught us a new method for the preparation of thiolocarboxylic acids through reaction of organo-magnesium compouds with carbon oxysulfide.]

In 1910, Bloch *et al.* (145) supplemented Houben's historical remarks:

> E. Lippmann und F. Fleissner[2] (*146*) haben bereits 1888 einige Vertreter dieser Körperklasse....erhalten und auch analysiert, so die Dithiooxychinolincarbonsäure, HOC_9H_5 N.CS.SH. Sie entsteht beim Erhitzen von o-Oxychinolinkalium mit Schwefelkohlenstoff in Gegenwart von Alkohol, auch durch Erhitzen von o-Chinolin mit Kaliumxanthogenat und Alkohol bei 100°. Aus Resorcin ergibt die Einwirkung von Kaliumxanthogenat und Alkohol die Dithioresorcylsäure, $(HO)_2C_6H_2$.CS.SH, welche bereits 1883 von Cyrill Reichl[1] (*147*) auf dem gleichen Wege dargestellt, analysiert und Resorcinxanthogein genannt worden war. Im folgenden Jahr beschreibt Lippmann[2] (*148*) die letztere Säure ausführlicher und gibt gleichzeitig eine Charakteristik der Dithiopyrogallolcarbonsäure, $C_6H_2(OH)_3$.CS.SH.
>
> [As early as in 1888, E. Lippmann and F. Fleissner[2] (*146*) have obtained and also analyzed several examples of this class of compounds, e.g. dithiooxyquinoline carboxylic acid, HOC_9H_5N.CS.SH. It is formed by heating of potassium o-oxyquinolinate with carbon disulfide in the presence of alcohol and also by heating of o-oxyquinoline with potassium xanthate and alcohol at 100°. Treatment of resorcinole with potassium xanthate and alcohol yields resorcinole dithiocarboxylic acid, $(HO)_2C_6H_2$.CS.SH, which has already been prepared in the same way, and analyzed by Cyrill Reichl[1] (*147*). In the following year Lippmann[2] (*148*) describes that acid more comprehensively and, at the same time, gives a characterization of pyrogallol dithiocarboxylic acid, $C_6H_2(OH)_3$.CS.SH.]

Bloch *et al.* (*145*) obtained arene dithiocarboxylic acids by treatment of aldehydes with hydrogen disulfide (hydrogen persulfide) in the presence of zinc chloride according to Equation (31). They also describe the alkylation of the salts to form the dithioesters (Equation (32)), and oxidation under formation of bis(thioacyl) disulfides (Ar−CS−S−S−CS−Ar):

$$\mathrm{Ar{-}CHO + H_2S_2 + ZnCl_2 \longrightarrow\longrightarrow Ar{-}CS{-}SK \longrightarrow Ar{-}CS{-}SH} \tag{31}$$

$$\mathrm{Ar{-}CS{-}SK + RX \longrightarrow Ar{-}CS{-}SR\ (R = Me, Et)} \tag{32}$$

In their paper of 1910, they claim to have prepared the dithiocarboxylic acids and esters already in 1901 and point out their method to represent an advantageous supplement of Houben's Grignard reaction which had been published in the meantime. In fact, Bloch and Höhn (*149*) had taken out a patent for their method in 1908.

In 1902 and in the following years Houben and co-workers described the successful synthesis of a series of aromatic (*136*, *143*) and aliphatic (*135*, *150*) dithiocarboxylic acids by use of the Grignard reaction (Equation (33), which until today represents one of the most important methods of preparation. His proposal to name the dithiocarboxylic acids as "Carbithiosäuren" ("carbithioic acids"), on the other hand, has not prevailed.

$$\begin{gathered}\mathrm{R{-}MgX + CS_2 \longrightarrow R{-}CS_2MgX \xrightarrow{H_3O^+} R{-}CS{-}SH}\\ \mathrm{R = C_6H_5, C_6H_5CH_2, 1-C_{10}H_7, 4-Br-C_6H_4}\end{gathered} \tag{33}$$

He specified the properties of these dithiocarboxylic acids as follows (*136*):

> Die Dithiosäuren sind lebhaft gelb, roth oder violett gefärbte Oele — bekanntlich gehört der CS-Rest zu den chromophoren Gruppen — in freiem Zustande ziemlich unbeständig und starke Säuren... Am leichtesten lassen sie sich durch ihre Schwermetallsalze charakterisiren, die zum Theil durch eine ausserordentliche Löslichkeit in organischen Lösungsmitteln... ausgezeichnet sind.
>
> [The dithioacids are vividly yellow, red or violet colored oils — as everybody knows the CS residue belongs to the chromophorous groups — rather unstable in the free state and strong acids... They can be most simply characterized through their heavy metal salts which are excellently soluble in organic solvents in many cases.]

At first, Houben did not obtain esters of the dithiocarboxylic acids. But in two later papers, he described the preparation of methyl and ethyl dithioacetate, dithiopropionate and α-dithionaphthoate by alkylation of the corresponding magnesium dithiocarboxylates (obtained from Grignard reactions) with dialkyl sulfates equation (34) (*151*).

$$\begin{array}{l} R^1{-}CS_2MgX + R^2{-}Y \longrightarrow R^1{-}CS{-}SR^2 \\ R^1 = Me, Et, PhCH_2, 1 - C_{10}H_7, R^2 = Me, Et \end{array} \tag{34}$$

Thus, although Houben was really a pioneer in the field of dithiocarboxylic acid chemistry, not all of the previous publications had been obsolete as Bloch *et al.* (*145*) pointed out. In particular, Lippmann and co-workers (*146*, *148*) undoubtedly had prepared and well characterized hydroxyarenedithiocarboxylic acids and their esters. On the other hand, Gabriel and Leupold's result on dithiophthalide (*137*), which Houben had accepted to be correct, raises doubts because he described it as *farblose oder schwach röthliche... Blättchen* (colorless or faintly reddish... platelets), whereas later authors expectedly found the pure compound to be definitely red-colored (*152*) and also Meyer's diphenyldithiophthalide (*138*) as well as dimethyldithiophthalide (*153*) are red.

8. Thioamides

As early as 1815, Gay-Lussac (*154*) prepared the first thiocarboxylic acid amide by reaction of dicyanogen with hydrogen sulfide according to Equation (35).

$$N{\equiv}C{-}C{\equiv}N + H_2S \longrightarrow N{\equiv}C{-}CS{-}NH_2 \tag{35}$$

It was named *Flaveanwasserstoff* (flaveanic acid) by Berzelius on account of its bright yellow color (*155*) and exhibits the structure of oxalonitrile-thioamide $H_2N{-}CS{-}C{\equiv}N$. Its counterpart the red dithiooxamide $H_2N{-}CS{-}CS{-}NH_2$ was, again by Berzelius, called *Rubeanwasserstoff* (rubeanic acid) (*155*). It was prepared in a similar way in 1825 by Wöhler and Liebig (*156*). These two thioamides of oxalic acid thus actually rank among the earliest discovered organosulfur compounds. Dithiooxamide was characterized in more detail by Völckel (*157*) who also pointed out its chemical analogy with oxamide and thereby provided the first structural proof in the class of thioamides. Berzelius's names indicate that the protons of the NH_2 groups in these thioamides can be exchanged by metal ions under formation of salts. They exhibit acidic character as all thioamides do and even more pronounced than amides.

In 1848, Cahours (*158*) prepared thiobenzamide from benzonitrile and hydrogen sulfide. Later on (1868), Hofmann obtained naphthalene-1-thiocarbamide ("Menaphtothiamid") from α-naphthonitrile (*159*) and 4-aminothiobenzamide from 4-nitrobenzonitrile (*160*). In 1878 Bernthsen (*161*) comprehensively studied this type of reaction and summarized the above-mentioned results of Gay-Lussac, Wöhler, Cahours, Hofmann as well as earlier reports of Weddige on $EtO{-}CO{-}CS{-}NH_2$ (*162*), Czumpelik (*163*), and Wanstrat (*164*) on this topic. Bernthsen prepared phenylacetothioamide (*161*, *165*) and thioacetamide $CH_3{-}CS{-}NH_2$, the prototype of the aliphatic series (*166*), from the corresponding nitriles. In addition, he found out that amidines could be transformed into different types of thioamides either with hydrogen sulfide or carbon disulfide (*166*, *167*), (see Equations (36)–(38)).

$$\begin{array}{r} R{-}C({=}NH){-}NHPh + H_2S \longrightarrow R{-}CS{-}NHPh \\ R = H, Me, Ph \end{array} \tag{36}$$

$$\mathrm{R{-}C({=}NPh){-}NHPh + H_2S \text{ or } CS_2 \longrightarrow R{-}CS{-}NHPh} \qquad \mathrm{R = H, Ph} \tag{37}$$

$$\mathrm{R{-}C({=}NH){-}NPh_2 + CS_2 \longrightarrow R{-}CS{-}NPh_2} \qquad \mathrm{R = H, Ph} \tag{38}$$

Bernthsen (*161*) also investigated the fundamental chemical reactions of the thioamides such as hydrolysis, thermolysis, alcoholysis, and reduction with sodium amalgam, which leads to amines. As a result, he could answer the question of tautomerism and he clearly pointed out that the compounds exhibit the thionocarboxamide rather than the thiolocarboximide structure (*161*).

The nitrile/hydrogen sulfide procedure and, in addition, the thionation of amides with phosphorus pentasulfide, which was introduced by Hofmann (*168*) in 1878, have remained important methods for the preparation of thioamides until now, (*103*, *169*). Hofmann (*168*) anticipated this when he wrote:

> Die Methode ist sicherlich in vielen Fällen anwendbar, möglicher Weise ganz allgemein für die Ueberführung der Amide in die entsprechenden Thioverbindungen.
>
> [The method is surely applicable in many cases, possibly quite generally for the transformation of the amides into the corresponding thiocompounds].

He applied his method on the preparation of exemplary compounds of the series such as thioformamide $\mathrm{H{-}CS{-}NH_2}$, thioacetamide $\mathrm{CH_3{-}CS{-}NH_2}$, thioformanilide $\mathrm{H{-}CS{-}NH{-}Ph}$, and thioacetanilide $\mathrm{CH_3{-}CS{-}NH{-}Ph}$. Hofmann (*170*) also discovered the reaction of phenyl isocyanide with hydrogen sulfide, which leads to thioformanilide according to Equation (39).

$$\mathrm{Ph{-}N{=}C + H_2S \longrightarrow Ph{-}NH{-}CH{=}S} \tag{39}$$

As mentioned above, Sachs and Loevy (*144*) obtained *N*-substituted thioamides by Grignard reaction of isothiocyanates with alkyl- and phenylmagnesium iodides according to Equation (40).

$$\mathrm{R^1{-}N{=}C{=}S + R^2{-}MgI \longrightarrow} R^1\mathrm{{-}NH{-}CS{-}R^2} \tag{40}$$

9. Thiocarbonic acid and its derivatives

Although numerous members of this class of compounds have been discovered in the first half of the nineteenth century, the extraordinary diversity of thiocarbonic acid derivatives, in particular of the nitrogen derivatives, cannot be treated here in completeness. Therefore, only prototypical examples will be dealt with.

9.1. *Mono- and dithiocarbonic acid derivatives*

The free mono- and dithiocarbonic acids are unknown until now. But their esters were prepared in the early nineteenth century. In 1873, Salomon (*171*) summarized the chemistry of all possible types of thiocarbonic acids esters. He himself described the synthesis of *O*,*S*-diethyl thiocarbonate $\mathrm{EtO{-}CO{-}SEt}$ from ethoxycarbonyl chloride and sodium ethanethiolate, or by alkylation of potassium ethoxycarbonylthiolate with bromoethane. He pointed out that this ester was an isomer of O,O'-diethyl thiocarbonate $\mathrm{EtO{-}CS{-}OEt}$, which Debus (*172*) had already isolated decades before from the mixture of products formed by thermolysis of bis(ethoxythiocarbonyl) disulfide $\mathrm{EtO{-}CS{-}S{-}S{-}CS{-}OEt}$ (dixanthogene). It could be also prepared in a more straightforward way (*171*) from potassium ethoxide and thiophosgene.

9.2. *Thiophosgene*

This compound was first described by Kolbe in 1843 (*173*), who had prepared it by room temperature chlorination of carbon disulfide according to Equation (41).

$$CS_2 + 2Cl_2 \longrightarrow CSCl_2 + SCl_2 \tag{41}$$

Kolbe recognized the analogy of thiophosgene with phosgene:

> . . . würde also dieser Körper die dem Chlorkohlenoxyd analoge Schwefelverbindung seyn und seine Zusammensetzung durch die Formel $CSCl_2$ ausgedrückt werden.
>
> [. . . this body would thus represent the sulfur compound which is the analog of chlorocarbon oxide and its composition would be expressed by the formula $CSCl_2$].

9.3. *Xanthates*

As early as in 1822, Zeise (*174*) had already prepared potassium *O*-ethyl dithiocarbonate (potassium xanthate) according to Equation (42). He also isolated the corresponding free acid EtO−CS−SH (xanthic acid) as a labile oil decomposing at 25°C (Equation (42)) (*175*) and discovered thiocarbamic acid $H_2N{-}CS{-}SH$, which he prepared by action of ammonia on carbon disulfide (*176*).

$$\begin{aligned} CS_2 + EtOK \longrightarrow EtO{-}CS_2^-K^+ &\xrightarrow{H_2SO_4} EtO{-}CS{-}SH \\ EtO{-}CS_2^-K^+ &\xrightarrow{EtX} EtO{-}CS{-}SEt \end{aligned} \tag{42}$$

The corresponding asymmetric dithioester EtO−CS−SEt (ethyl xanthate) was obtained from the above-mentioned mixture which is produced by thermolysis of dixanthogene (*172*, *177*, *178*), and by alkylation of potassium xanthate with chloroethane (*172*) or better with bromoethane (Equation (42)) (*171*). Zeise (*174*) coined the generic trivial name xanthate (*xanthür*) for this class of compounds due to the yellow color (from Greek: *xanthos*–yellow) of certain xanthate salts, notably copper(I) xanthate, and the fact that xanthic acid stains the skin yellow. The diethyl ester is, however, a colorless liquid. The name xanthate is still in use. Cellulose xanthate, *e.g.*, plays an important role as the soluble intermediate for the technical production of the valuable semi-synthetic regenerated cellulose fiber viscose.

The symmetric counterpart EtS−CO−SEt of ethyl xanthate was first described by Schmitt and Glutz in 1868 (*179*), who obtained it by treatment of ethyl thiocyanate with sulfuric acid. Later on, Salomon (*171*) prepared it from phosgene and potassium ethanethiolate.

Salomon (*180*) also, for the first time, prepared *S*-ethyl thiocarbamate $EtS{-}CO{-}NH_2$ (thiourethane) in a straightforward way from (ethylthio)carbonyl chloride and ammonia, whereas Debus obtained its isomer *O*-ethyl thiocarbamate $EtO{-}CS{-}NH_2$ (thionourethane, xanthogenamide) by ammonolysis of dixanthogene (*181*) or diethyl xanthate (*172*).

9.4. *Trithiocarbonic acid*

Trithiocarbonic acid HS−CS−SH was found to be an isolable, although easily decomposing, evil-smelling red oil. Berzelius (*182*) and Zeise (*176*) prepared it from potassium trithiocarbonate, which salt could be alkylated to form diethyl trithiocarbonate (Equation (43)) (*171*, *172*, *183*).

Klason (*184*) obtained the ester also from thiophosgene and sodium ethanethiolate (Equation (44)).

$$CS_2 + K_2S \longrightarrow K_2CS_3 \xrightarrow{H_3O^+} HS{-}CS{-}SH$$

$$K_2CS_3 \xrightarrow{EtX} EtS{-}CS{-}SEt \qquad (43)$$

$$CSCl_2 + 2EtSNa \longrightarrow EtS{-}CS{-}SEt + 2NaCl \qquad (44)$$

Klason (*57*) also synthesized tetraethyl tetrathioorthocarbonate from tetrachloromethane and sodium ethanethiolate, and oxidized it to ethanesulfonic acid (Equation (45)).

$$CCl_4 + 4EtSNa \longrightarrow C(SEt)_4 \xrightarrow{HNO_3} Et{-}SO_3H \qquad (45)$$

9.5. *Thiourea*

In 1869, Reynolds (*185*) performed a systematic study on the rearrangement of ammonium thiocyanate to thiourea, which was an unknown compound till then, whereas N-substituted thiourea derivatives had already been prepared from isothiocyanates (see below). Reynolds was convinced that this reaction should take place according to Equation (46) in analogy to Wöhler's famous and significant transformation of lead and ammonium cyanate into urea (*186*). He found out that a temperature of 170°C is necessary to achieve the reaction. Thus, thiourea, in contrast to urea, is not formed in boiling aqueous solution.

$$NH_4SCN \xrightarrow{170^\circ C} H_2N{-}CS{-}NH_2 \qquad (46)$$

Reynolds realized the importance of his discovery. He made clear that thiourea and ammonium thiocyanate are definitely different compounds, whereas the failure of Liebig (*187*) and Völckel (*188*) to rearrange ammonium thiocyanate had led contemporary chemists, notably Hofmann (*189*), to the opinion that … *sulfocyansaures Ammonium die dem Harnstoff entsprechende Schwefelverbindung sei, welche jedoch eine besonders ausgesprochene salzartige Constitution besitze.* [… ammonium sulfocyanate be the sulfur compound analogous with urea, which, however, exhibits a particularly pronounced salt-like constitution.] (*185*, *189*). Reynolds wrote:

> Betrachten wir den sauerstoffhaltigen Harnstoff als Carbamid…, so müssen wir den schwefelhaltigen Harnstoff als Sulfocarbamid… betrachten
>
> [If we look upon the oxygen containing urea as carbamide… we must look upon the sulfur containing urea as thiocarbamide…]

9.6. *Isothiocyanates*

A valuable survey on the history of the isothiocyanates (mustard oils) can be found in Gildemeister's handbook (*190*).

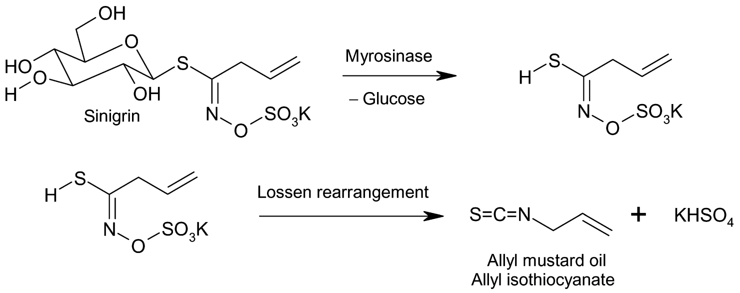
Isothiocyanates are natural products. They frequently occur in plants, mostly in *brassica* species, which normally contain the corresponding conjugates with carbohydrates ("glucosinolates") (*191*). The volatile oil of mustard, mustard oil (allyl isothiocyanate), is particularly well known and important. Already ancient (Dioscorides, Plinius) and mediaeval authors (Theophrastus) recognized the medicinal activity of the mustard spice (*190*). Mustard, mustard seeds, and the mustard plant, which was obviously grown systematically in ancient times, are even symbolically mentioned in the Bible:

> Evangelium Matthaei, 13: 31:
>
> Das Himmelreich ist gleich einem Senfkorn, das ein Mensch nahm und säte es aus auf seinem Acker; welches das kleinste ist unter allem Samen; wenn es aber erwächst, so ist es das größte unter dem Kohl und wird ein Baum, daß die Vögel unter dem Himmel kommen und wohnen unter seinen Zweigen.
>
> [The Kingdom of Heaven is like a mustard seed, which is the tiniest of all seeds, which a men took and sowed it on his field; but which becomes the largest of all cabbage plants and becomes a tree where the birds beneath heaven will come and will live beneath its branches.]

Charles the Great gave instruction in his *Capitulare* of 812 as to grow mustard in the Franconian Empire. Porta in 1608 observed an oil being formed on distillation of mustard seeds with water (*190*).

The generic trivial name mustard oils for the compound class of the isothiocyanates was coined by Hofmann (*192*) with reference to the natural allyl mustard oil, which must not be confounded with the chemical weapon mustard gas (Lost), bis(2-chloroethyl) sulfide, (see above)!

Allyl isothiocyanate is obtained by steam distillation of mustard seeds. During this procedure, it is formed by enzymatic cleavage of the *S*-glucoside sinigrin with myrosinase and subsequent cleavage and Lossen rearrangement of the intermediate thiohydroximic acid *O*-sulfonate according to Scheme 4 (*190*, *191*):



Scheme 4.

In 1732, Boerhave isolated and characterized this volatile oil (*190*). Thibierge recognized its sulfur content (1819) (*190*), and Dumas and Pelouze (*193*) performed the first elemental analysis in 1833. Since they obtained too low sulfur contents for allyl isothiocynate and allylthiourea they assumed oxygen contents of ca. 10% for the two compounds. This resulted in the strange elemental formulae $C^{16}H^{10}N^{2}S^{5/4}O^{5/4}$ and $C^{16}H^{16}N^{4}S^{5/4}O^{5/4}$, respectively, whereby of course the early atomic weights have to be considered. They also discovered the reaction of mustard oil with ammonia to form allylthiourea (thiosinamine) according to Equation (49), ($R^1 = -CH_2CH{=}CH_2$, $R^2 = H$). Later on, Hofmann (*192*) performed comprehensive investigations on the preparation of organic isothiocyanates from amines and carbon disulfide *via* the corresponding N, N'-dialkyl thioureas (Equation (47)) or, more convenient in the aliphatic series, from silver dithiocarbamates (Equation (48)):

$$\mathrm{CS_2 + 2RNH_2 \longrightarrow RNH{-}CS_2^- RNH_3^+ \longrightarrow RNH{-}CS{-}NHR \longrightarrow R{-}N{=}C{=}S} \tag{47}$$

$$\mathrm{R{-}NH{-}CS_2^- RNH_3^+ \longrightarrow R{-}NH{-}CS_2^- Ag^+ \longrightarrow R{-}N{=}C{=}S} \tag{48}$$

Hofmann also clarified the question of isomerism between the isothiocyanates and the thiocyanates. Reduction of the alkyl isothiocyanates with zinc led to alkylamines, whereas alkyl thiocyanates gave the corresponding alkanethiols. Thus, the alkyl substituent must be linked to nitrogen in the former but linked to sulfur in the latter compounds (*192*). Furthermore, he prepared quite a number of *N*-substituted thioureas from isothiocyanates and ammonia or amines according to Equation (49) (*189*, *192*, *194*), which is the reverse reaction of the last step in Equation (48).

$$R^1{-}N{=}C{=}S + R^2{-}NH_2 \longrightarrow R^1{-}NH{-}CS{-}NH{-}R^2 \tag{49}$$

In 1875, it was shown that alkyl thiocyanates are easily rearranged into the corresponding isothiocyanates (*195*, *196*). According to Gerlich's observations (*196*), the isomerization of allyl thiocyanate takes even place at ambient temperature:

> Im Sommer muss die Aufbewahrung, wenn das Präparat vollständig senfölfrei bleiben soll, im Eiskeller geschehen, der Winter ist für die Darstellung geeigneter.
>
> [During summer times, the storage must take place in an ice-cellar if the compound shall remain free of mustard oil. The winter season is more suitable for the preparation.]

10. *S*-oxidized organosulfur compounds

As mentioned above, sulfur can be easily oxidized to higher oxidation states since it belongs to the third row of the periodic table of elements. The violation of the octet rule ("hypervalency") is therefore possible. Accordingly, numerous *S*-oxidized sulfur compounds exist. These were already well known to a large extent in the nineteenth century and aroused the interests of the synthetic chemists as well as of those organic chemists devoted to theory.

Sulfoxides represent the simplest type of these hypervalent sulfur compounds. The prototype of the aliphatic series, dimethyl sulfoxide, was the first example to be prepared. Cahours obtained it in 1865 from dimethyl sulfide *via* the dibromide according to Equation (50) (*96*).

$$Me_2S + Br_2 \longrightarrow Me_2SBr_2 \xrightarrow{Ag_2O} Me_2S{=}O \tag{50}$$

In 1867, Saytzeff (*197*) obtained dimethyl and diethyl sulfoxide by oxidation of the corresponding sulfides with nitric acid. Beckmann studied this oxidation reaction (Equation (51)), of symmetric and asymmetric sulfides. He systematically varied the primary and secondary alkyl groups R^1 and R^2 including ethyl phenyl sulfide and 1,2-bis(ethylthio)ethane and found out that sulfoxides and/or the corresponding sulfones are formed depending on the nature of R^1 and R^2 and on the reaction conditions (*198*).

$$R^1{-}S{-}R^2 + HNO_3 \longrightarrow R^1{-}SO{-}R^2 \longrightarrow R^1{-}SO_2{-}R^2 \tag{51}$$

Colby and McLoughlin (*199*) synthesized diphenyl sulfoxide, the prototypical aromatic derivative, in an entirely different way by a Friedel-Crafts-type electrophilic acylation of benzene with sulfur dioxide under the catalysis with aluminum chloride according to Equation (52).

$$C_6H_6 + SO_2 \xrightarrow{AlCl_3} C_6H_5{-}SO{-}C_6H_5 \tag{52}$$

The sulfoxides were regarded as analogs of the ketones, although this analogy is a rather formalistic one and is only to some extent in agreement with the chemical behavior of the sulfoxides. Furthermore, sulfoxides are not planar molecules. Unlike the carbonyl compounds, they exhibit a pyramidal structure as the sulfonium ions do (see Section 5). As a consequence, sulfoxides with two different substituents are chiral. They can be resolved into two enantiomers, which has been demonstrated in 1926 for $R^1{-}SO{-}R^2$ with $R^1 = 4{-}Me{-}C_6H_4$, $R^2 = 4{-}H_2N{-}C_6H_4$ and $R^1 = Me$, $R^2 = 2{-}HO_2C{-}C_6H_4$ by use of the classical method, *i.e.* the separation of the diastereoisomeric camphorsulfonates and menthylammonium salts (*200*).

Sulfones, the species with the next higher oxidation state, have been known even before the sulfoxides. Already in 1834, Mitscherlich (*201*) prepared diphenyl sulfone by reaction of benzene with smoking sulfuric acid according to Equation (53).

$$C_6H_6 + H_2SO_4(SO_3) \longrightarrow C_6H_5{-}SO_2{-}C_6H_5 + C_6H_5{-}SO_3H \qquad (53)$$

The aliphatic diethyl sulfone was obtained by von Öfele (*202*) through harsh oxidation of diethyl sulfide with red smoking nitric acid according to Equation (54).

$$C_2H_5{-}S{-}C_2H_5 + HNO_3(N_2O_5) \longrightarrow C_2H_5{-}SO_2{-}C_2H_5 \qquad (54)$$

10.1. *Sulfenic acids and their derivatives*

Sulfenic acids $R{-}S{-}OH$ are extremely labile compounds, whereas their oxygen analogs, the alkyl hydroperoxides $R{-}O{-}OH$, are well-known compounds (cumyl hydroperoxide $Ph{-}CMe_2{-}O{-}OH$ is even an industrial intermediate) and also the alkyl hydrodisulfides $R{-}S{-}SH$ are more stable. Only by the end of the twentieth century, Japanese research groups were able to synthesize trypticene-9-sulfenic acid (*203*) and *trans*-decaline-9-sulfenic acid (*204*) and to isolate aromatic sulfenic acids, which were stabilized by extremely pronounced steric shielding, not to say encapsulation, of the functional $-S{-}OH$ group (*205*). Functional derivatives of sulfenic acids such as the esters $R^1{-}S{-}OR^2$, amides $R{-}S{-}NR_2$, and sulfenyl chlorides $R{-}S{-}Cl$, on the other hand, including the sulfenate anions $R{-}S{-}O^-$ (*206*) have been well known for a long time.

10.2. *Sulfinic acids and their derivatives*

Ethanesulfinic acid was discovered in 1857 by Hobson (*207*) who obtained it, as an aqueous solution, by reaction of diethylzinc with sulfur dioxide *via* the zinc and the barium salts. In the same way (Equation (55)), he prepared methanesulfinic acid (*208*). Wischin (*209*) confirmed Hobson's result and proved the constitution of the ethanesulfinate as Hobson had found a somewhat deviating elemental analysis for $(EtSO_2)_2Ba$.

$$\begin{aligned} &R_2Zn + 2SO_2 \longrightarrow (RSO_2)_2Zn \longrightarrow (RSO_2)_2Ba \longrightarrow RSO_2H \\ &R = Me, Et \qquad (55) \end{aligned}$$

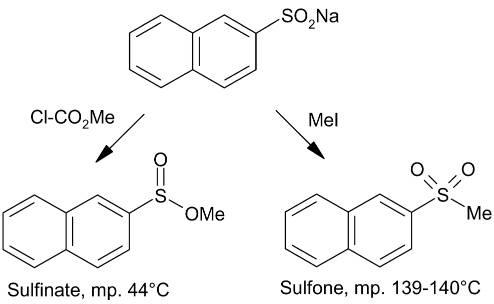
Benzenesulfinic acid (*Benzylschweflige Säure*, see above, thiophenol), $C_6H_5{-}SO_2H$, and its salts were prepared for the first time in 1861 by Kalle (*210*) through reaction of benzenesulfonyl chloride (Benzylsulfonchlorid) with diethylzinc (Equation (56)). The expected diphenyl sulfone or ethyl-phenyl sulfone were, however, not formed by this reaction.

$$\begin{aligned} &2Ph{-}SO_2{-}Cl + Et_2Zn \longrightarrow (Ph{-}SO_2)_2Zn + 2Et{-}Cl \\ &(Ph{-}SO_2)_2Zn + H_3O^+ \longrightarrow Ph{-}SO_2H \qquad (56) \end{aligned}$$

The same compound was also formed by the disproportionation of diphenyl disulfide with potassium hydroxide according to Equation (57), as Schiller and Otto found out (*38*):

$$Ph{-}S{-}S{-}Ph + KOH \longrightarrow PhSK + Ph{-}SO_2K \qquad (57)$$

Otto and Rössing (*211*) have prepared impure alkyl benzenesulfinate from sodium benzenesulfinates and alkoxycarbonyl chlorides in 1885/1886. Since Baumann (*212*) doubted the sulfinate structure of the compounds and regarded them as sulfones, the authors prepared the pure crystalline methyl naphthalene-2-sulfinate and proved it to be definitely different from the isomeric



Scheme 5.

sulfone (Scheme 5) (*213*). Expectedly, the sulfinate ester could be saponified with alkali in contrast to the sulfone (*213*).

Still in 1925, Phillips recognized methyl naphthalene-2-sulfinate to be the only pure ester of a sulphinic acid which has hitherto been described. He prepared ethyl *p*-toluenesulfinate (Equation (58)) and succeeded in resolving it into the two enantiomers *via* re-esterification with *l*-menthol since sulfinates are chiral too, as the sulfoxides are (*214*).

$$4-\mathrm{Me{-}C_6H_4{-}SO{-}Cl} + \mathrm{EtOH} \longrightarrow (d,l)-4-\mathrm{Me{-}C_6H_4{-}SO{-}OEt} \qquad (58)$$

10.3. *Sulfonic acids and their derivatives*

Methanesulfonic acid was first prepared in 1845 by Kolbe (*215*) who used the sophisticated and ingenious reductive dechlorination of potassium trichloromethanesulfonate by stepwise electrolysis (*via* the dichloro- and monochloromethanesulfonate) at zinc cathodes or with potassium amalgam. He prepared the precursor by alkaline hydrolysis of trichloromethanesulfonyl chloride (*215*), which Berzelius and Marcet (*7*) had already obtained 30 years before from carbon disulfide and wet chlorine (Equation (59)).

$$\mathrm{CS_2} + \mathrm{Cl_2/H_2O} \longrightarrow \mathrm{CCl_3{-}SO_2Cl} \xrightarrow{\mathrm{KOH}} \mathrm{CCl_3{-}SO_3^-K^+} \xrightarrow{\mathrm{Red}} \mathrm{CH_3{-}SO_3^-K^+} \longrightarrow \mathrm{CH_3{-}SO_3H} \qquad (59)$$

Alkanesulfonic acids were, of course, also obtained by oxidation of suitable precursors such as thiols (Equation (60) (*216*), Equation (61) (*26*), Equation (62) (*35*)), disulfides (Equation (63) (*217*)), thiocyanates (Equation (*64*) (*218*)), and sulfinates (Equation (65) (*219*)). The oxidation of 2-mercaptoethanol (*46*) and cystine (*47*) to form 2-hydroxyethanesulfonic acid (isaethionic acid) as well as the oxidation of cysteine to cysteic acid and decarboxylation of the latter to taurine (*48*) has already been discussed in Section 3 with regard to the structural elucidation of the two aminoacids.

$$\mathrm{C_2H_5{-}SH} + \mathrm{HNO_3} \longrightarrow \mathrm{C_2H_5{-}SO_3H} \qquad (60)$$

$$\mathrm{CH_2{=}CH{-}SH} + \mathrm{HNO_3} \longrightarrow \mathrm{CH_2{=}CH{-}SO_3H} \qquad (61)$$

$$\mathrm{CH_3{-}CH(SH){-}CO_2H} + \mathrm{HNO_3} \longrightarrow \mathrm{CH_3{-}CH(SO_3H){-}CO_2H} \qquad (62)$$

$$\mathrm{CH_3{-}S{-}S{-}CH_3} + \mathrm{HNO_3} \longrightarrow \mathrm{2CH_3{-}SO_3H} \qquad (63)$$

$$\mathrm{R{-}SCN} + \mathrm{HNO_3} \longrightarrow \mathrm{R{-}SO_3H}$$
$$\mathrm{R} = \mathrm{Me, Et} \qquad (64)$$

$$\mathrm{C_2H_5{-}SO_2Na(H)} + \mathrm{HNO_3} \longrightarrow \mathrm{C_2H_5{-}SO_3H} \qquad (65)$$

Buckton and Hofmann (*220*) studied the reactions of aliphatic amides and nitriles with concentrated sulfuric acid and sulfur trioxide, which led to sulfonic acids according to Equation (66):

$$\mathrm{R{-}CH_2{-}CONH_2/R{-}CH_2{-}CN + H_2SO_4/SO_3 \longrightarrow R{-}CH(SO_3H)_2 + R{-}CH(SO_3H){-}CO_2H}$$
$$\mathrm{R = H, Me} \qquad (66)$$

The obvious method for the preparation of aliphatic sulfonic acids, namely the nucleophilic substitution of alkyl halides with sulfite anions was explored later on by Strecker and his co-workers. In this way, they obtained methanesulfonic (*221*), ethanesulfonic (*222*, *223*), methanedisulfonic acid (*222*), and the like.

Taurine (2-aminoethanesulfonic acid) $H_2N{-}CH_2{-}CH_2{-}SO_3H$ was first isolated from the natural product ox-gall (therefrom its name, Greek: *tauros* = bull) as early as 1824 (*224*). It is a constituent of the bile acid taurocholic acid (*225*, *226*), which is ubiquitous in animals of all kind. Demarçay (*225*) had determined the elemental formula of taurine to be $C_2H_7NO_5$ (in terms of modern atomic weights), which appeared strange to Dumas and Pelouze (*227*). They repeated the analysis but, to their surprise, they found the same figures and were unable to explain this result. Obviously, both authors had failed to notice and had thus not determined the sulfur content of taurine, the correct elemental formula of which is of course $C_2H_7NO_3S$ with nearly the same analytical C-, H-, and N-values. The amino group of taurine is linked to the carboxylic group of cholic acid by an amide bond. Its structure was proved by Strecker in 1854 (*228*), who was interested in the fundamental question of whether natural products could be obtained by synthetic means:

> Die künstliche Bildung der in der Natur sich findenden Stoffe kann man als das Ziel ansehen, nach welchem die organische Chemie strebt. Es läßt sich nicht läugnen, daß wir noch sehr weit davon entfernt sind, die complexeren Stoffe zusammensetzen zu können, während auf der anderen Seite mancherlei Producte des Pflanzen- oder Thierlebens auch aus der Hand des Chemikers hervorgingen. Seit Wöhler den Harnstoff aus Cyansäure und Ammoniak zusammensetzen lehrte, und damit zeigte, daß die in dem Organismus thätige chemische Kraft nicht verschieden ist von der chemischen Kraft außerhalb desselben, haben wir auch organische Stoffe von höherer Zusammensetzung künstlich erzeugen gelernt .... Ich habe verschiedene Versuche zur künstlichen Bildung des Taurins angestellt...
>
> [The artificial formation of substances found in nature may be regarded as the target which organic chemistry is aimed at. It cannot be denied that we are far from being able to put together the more complex substances while, on the other side, diverse products of the plants' and animals' lives have emerged from the chemist's hand. Since Wöhler taught us to put together urea from cyanic acid and ammonia, and thereby showed that the chemical power, which is active in an organism, is not different from the chemical power outside of it, we have learnt to produce organic substances of a higher composition artificially too... I have started several experiments aimed at the artificial formation of taurine...]

Strecker (*228*) designed an unequivocal synthesis of taurine from ethanol *via* the thermolysis of ammonium 2-hydroxyethanesulfonate (*229*) (*isäthionsaures Ammoniak*), (Equation (67)).

$$\mathrm{HO{-}CH_2{-}CH_2{-}SO_3^-NH_4^+ \xrightarrow{\Delta} H_2N{-}CH_2{-}CH_2{-}SO_3H} \qquad (67)$$

He resumes (*228*):

> Der durch Erhitzen von isäthionsaurem Ammoniak dargestellte Stoff ist also identisch mit dem aus Galle gewonnenen Taurine.
>
> [The compound prepared by heating ammonium isaethionate is thus identical with taurine obtained from bile acid].

Independently, Kolbe (*230*) prepared taurine from potassium isaethionate *via* silver 2-chloroethanesulfonate according to Equation (68).

$$\mathrm{HO{-}CH_2{-}CH_2{-}SO_3^-K^+ + PCl_5 \longrightarrow Cl{-}CH_2{-}CH_2{-}SO_2Cl}$$
$$\mathrm{Cl{-}CH_2{-}CH_2{-}SO_2Cl \longrightarrow Cl{-}CH_2{-}CH_2{-}SO_3^-M^+ \xrightarrow{NH_3} H_2N{-}CH_2{-}CH_2{-}SO_3H}$$
$$\mathrm{M^+ = Ag^+, NH_4^+} \qquad (68)$$

Arenesulfonic acids have been prepared before their aliphatic counterparts. The methods for their preparation were of course quite different from those applied in the aliphatic series, as one would expect from today's knowledge on aromatic compounds.

Due to the early discovery of naphthalene in 1819 (*231*), naphthalenesulfonic acid was the first sulfonic acid of the aromatic series to be prepared. In 1825, Faraday treated naphthalene with sulfuric acid and found out that two novel acids sulpho-naphthalic acids were formed (*232*). He isolated the characteristic barium salts (glowing sulphonaphthalate of baryta and flaming sulphonaphthalate of baryta) and determined their elemental analyses, which were corroborated by Wöhler (*156*) and, in particular, by Berzelius (*233*), who very thoroughly repeated and confirmed Faraday's experiments. Only in 1870, the complicated processes occurring during the sulfonation of naphthalene were clearified. By a systematic study, Merz and Weith found out that the α-isomer is predominantly formed at low temperature, whereas it rearranges at high temperature to form the thermodynamically more stable β-isomer *via* equilibration with free naphthalene. Merz attributed the observed isomerism to the two possible positions of the naphthalene system. He even correctly assigned the structures of the α- and the β-isomer, although he could not experimentally prove his assignments (*234*). Using oleum as reagent, Kimberly obtained a mixture of a mono- and a disulfonic acid. Any hints on the position of the substituents are missing in his publication, but according to the reported melting point (65°C) of the corresponding sulfonyl chloride he had had the α-isomer in hands (*235*).

In 1834, Mitscherlch (*201*) obtained benzenesulfonic acid besides diphenyl sulfone from benzene and oleum (SO_3/H_2SO_4), *i.e.* by an electrophilic substitution reaction, (*c.f.* Equation (53)). The corresponding ester $Ph{-}SO_2{-}OEt$ was only prepared decades later from phenyl sulfonyl choride and sodium ethoxide (*236*).

In 1865, Jaworsky (*237*) studied the reaction of toluene with sulfuric acid and described the formation of *Toluolschwefelsäure* (toluenesulfuric acid), which he isolated as its barium, lead, potassium, and sodium salt. Obviously, he had obtained only one isomer, namely the *para*-isomer according to the melting points of the corresponding derivatives. In particular, he prepared toluene-4-sulfonyl chloride (m.p. 68–70°C), which represents a most important reagent (tosyl chloride) until nowadays, ethyl toluene-4-sulfonate (m.p. 33°C), and toluene-4-sulfonamide (m.p. 140°C) (Equation (69)).

$$
\begin{aligned}
CH_3{-}C_6H_5 + H_2SO_4/SO_3 &\longrightarrow CH_3{-}C_6H_4{-}SO_3H \longrightarrow\longrightarrow CH_3{-}C_6H_4{-}SO_2Cl\\
CH_3{-}C_6H_4{-}SO_2Cl + EtOH &\longrightarrow CH_3{-}C_6H_4{-}SO_2OEt\\
CH_3{-}C_6H_4{-}SO_2Cl + NH_3 &\longrightarrow CH_3{-}C_6H_4{-}SO_2NH_2
\end{aligned}
\tag{69}
$$

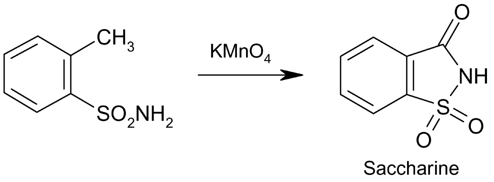
Four years later, Engelhardt and Latschinoff (*238*) recognized the formation of two isomers, which they were able to separate by fractionating crystallization of the potassium salts:

> Beim Erwärmen des Toluols mit Schwefelsäure bilden sich zwei isomere Toluolsulfonsäuren… Beim langsamen Erkalten der nicht zu sehr eingeengten Lösung scheiden sich zwei durch ihre Krystallform sich scharf unterscheidende Kaliumsalze aus. Das eine dieser Salze, welches α toluolsulfosaures Kalium ist, löst sich etwas schwerer in Wasser und krystallisiert in großen prismatischen Krystallen, das andere – β *toluolsulfosaures Kalium* – ist leichter in Wasser löslich und krystallisiert in lockeren, aus feinen Nadeln bestehenden Warzen.
>
> [Two isomeric toluenesulfonic acids are formed upon warming of toluene with sulfuric acid… Two potassium salts, which sharply differ in the shape of the crystals, are precipitating during slowly cooling down the not too much concentrated solution. One of these salts, which is α *potassium toluenesulfonate*, is somewhat more difficultly soluble in water and crystallizes in large prismatic crystals, the other one – β *potassium toluenesulfonate* – is easier soluble in water and crystallizes in loose warts of fine needles.]

Engelhardt and Latschinoff did, however, not assign distinct structures to their "α"- and "β"-isomers.

Only one further example out of the numerous arenesulfonic acids with substitutents at the ring should be mentioned here: the important industrial chemical sulfanilic acid. Shortly after the discovery of aniline (Unverdorben 1826, Runge 1834, Fritsche 1841), the reaction of this fascinating compound with sulfuric acid was investigated. Gerhardt obtained a low yield of the sulfonic acid by heating anilinium sulfate, which in fact represents the process (baking process) for the technical production of sulfanilic acid until nowadays. The same product was formed with improved yield by heating oxanilide or mixtures of oxanilide and formanilide with sulfuric acid (*239*). Gerhardt named the new, strong acid sulfanilic acid, a name which has survived till today.

Fahlberg and Remsen in 1879 (*240*) synthesized the cyclic imid of 2-carboxybenzenesulfonic acid (*Anhydroorthosulfaminbenzoesäure*) by oxidation of 2-methylbenzenesulfonamide with potassium permanganate according to Equation (70). This compound has, until today, remained in use as synthetic sweetener saccharine, which exhibits the 300-fold sweetness of saccharose. The two authors later on had a quarrel with each other about the priority and the question, who was the first of them to discover the sweetness of the compound (*241*).



(70)

10.4. *Thiocarbonyl* S*-oxides*

Thioamide S-oxides were the first S-oxides of thiocarbonyl compounds to be prepared. But even they could only be obtained and characterized in the twentieth century.

Kitamura in 1938 oxidized thiocarboxamides with hydrogen peroxide according to Equation (71) and assigned the structures of imidosulfenic acids (*Thioperimidsäuren*, thioperimidic acids) to the products. He also mentioned the tautomeric structures of thioamide S-oxides but could not furnish any proof for either of them (*242*).

$$R^1{-}CS{-}NH{-}R^2 + H_2O_2 \longrightarrow \underset{\text{Thioperimidic acid}}{R^1{-}C({=}NR^2){-}S{-}OH} \leftrightarrows \underset{\text{Thioamide } S\text{−oxide}}{R^1{-}C({=}SO){-}NH{-}R^2} \quad (71)$$

Only in 1960, Walter comprehensively investigated the prototype of the series, thioacetamide S-oxide [$CH_3{-}C({=}SO){-}NH_2$], which, by the way, turned out to be a significant carcinogen. He prepared it by oxidation with hydrogen peroxide (Equation (72)) and unequivocally proved its structure (*243*). In the following decade, his research group performed numerous synthetical and structural studies about the class of thioamide S-oxides.

$$CH_3{-}CS{-}NH_2 + H_2O_2 \longrightarrow CH_3{-}C({=}SO){-}NH_2 \quad (72)$$

The S-oxides ("sulfines") and S-dioxides ("sulfenes") of other thiocarbonyl compounds have been disclosed even later, *c.f.*, for instance Zwanenburg's review articles (*244*).

11. Concluding remarks

Unlike oxygen, the homologous element sulfur is not an indispensible constituent of the main classes of natural compounds such as the carbohydrates, the lipids, the proteins (with exceptions), the nucleic acids, the isoprenoids, the alkaloids, and others. Strictly spoken, the "original organic" compounds, *i.e.* compounds found in organisms, are rarely sulfur compounds. In particular, naturally occurring organic sulfur compounds only in exotic cases simply represent the analogs of the corresponding "normal" oxygen compounds (*245*). Rather, they exhibit quite different structures and belong to peculiar compound classes such as the disulfides, the isothiocyanates, or the sulfonic acids (taurine).

However, the history of organosulfur compounds is of course, nevertheless, embedded in the context of the evolution of organic chemistry and, moreover, in the general history of science. As we have frequently emphasized in this article, organic sulfur compounds have played a significant role for the development of the chemical theory. Thus, Schaumann's statement (*246*): *Sulfur is more than the fat brother of oxygen*, concerning the chemical behavior, is valid for the historical significance as well.

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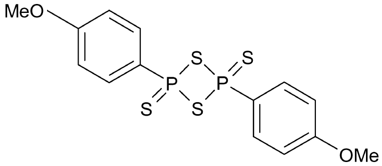
(103) It should be mentioned that nearly a century later 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide:



proved to be advantageous for the transformation of carbonyl compounds into the corresponding thiones as compared with phosphorus pentasulfide. The use of this reagent for the preparation of thiobenzophenone and thiocamphor from the corresponding ketones was first describend in 1967 by Hoffmann and Schumacher (*104*). A decade later, Lawesson's group comprehensively and with great success explored its suitability for the thionation of ketones (*105*), esters, thiolesters and amides, and finally its name "*Lawesson's reagent*" has been coined.

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