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HEAVY-METAL DETOXIFICATION USING SULFUR COMPOUNDS

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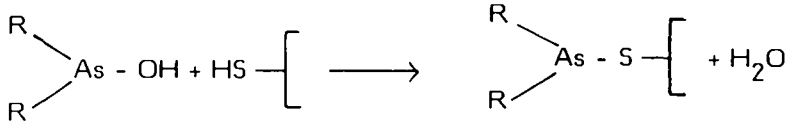
The development of sulfur compounds for use in heavy-metal detoxification has resulted in the preparation and use of compounds which are highly effective for this purpose because of the great stability of many types of metal-sulfur linkages. The ability of many of these compounds to penetrate cellular membranes has made them useful in situations in which the more readily ionized oxygen based chelating agents are quite ineffective. This review describes the use of mono-, di-, and polythiols, cysteine derivatives, and dithiocarbamates for the detoxification of arsenic, mercury, lead, cadmium, and copper, with some attention to other types of sulfur compounds and other toxic metals.

CONTENTS

I. HISTORICAL INTRODUCTION

While numerous fanciful reports of antidotes for toxic metals may be found in the medical literature prior to 1900, the development of effective antidotes for toxic metals is a relatively recent development. The line of experiments which have led to many of these may be traced to a hypothesis of the German scientist Paul Ehrlich, who searched for means of selectively poisoning the spirochete which caused syphilis in such a manner as to cure, rather than poison the human who was the host animal.[1] Ehrlich proved that a large number of arsenic-containing organic compounds could be used for this purpose, though they invariably were capable of producing at least some of the symptoms of arsenic poisoning in humans. Erhlich hypothesized that the mode of action of such drugs was via the reaction of the arsenic with the -SH groups present in enzymes needed for survival by the spirochete. This general idea can be summarized as

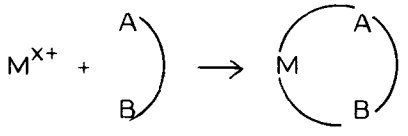


organoarsenic compound | HS-containing enzyme (functioning) | non-functioning enzyme

In subsequent studies on the action of organoarsenic compounds on trypanosomes, Voegtlin showed that this action can be prevented by glutathione, cysteine, and other compounds whose common feature is the presence of an -SH group.[2] Voegtlin also carried out a series of studies in which he demonstrated that certain simple thiols were capable of antagonizing the action of a lethal dose of arsenic(III) in animals for a limited period of time. These compounds were all capable of being metabolized quite rapidly by the mammalian body, but none of them contained two -SH groups in positions which would allow them to form a stable chelate ring with the arsenic which they bound. Voegtlin's results were promising, but they did not produce a compound which could be used effectively with humans suffering from arsenic intoxication. His work did clearly demonstrate that the toxicity of arsenic could be modified *in vivo* however, even if only temporarily, by treatment with appropriate compounds containing -SH groups. As a result of this work it was apparent that it might be possible to develop an effective antidote for arsenic if a suitable sulfhydryl-containing compound could be found which could form a stable complex with arsenic.

By the 1940's, evidence had been developed that some of the chelating agents which had been developed by analytical chemists were capable of tying up metal ions

in vivo:

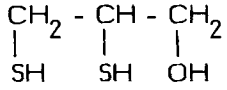


and that the resultant complexes could be much less toxic than the parent metal ion.[3,4] It was also realized that one type of antidote for a toxic metal would be a compound that would react with it to form a complex which would be excreted in the urine. These ideas were applied as early as the 1920's in the development of less toxic antimony-containing drugs for use in the treatment of schistosomiasis.[3] During the 1940's the notion that sulfur-containing molecules could form stable, more readily excretable complexes with toxic metals was reduced to practice by the development of BAL (2,3-dimercaptopropanol) as an antidote for arsenic.

In the animal experiments described below the route of administration is intraperitoneally unless mentioned otherwise.

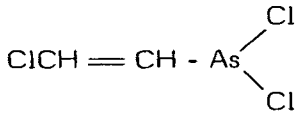
II. THE DEVELOPMENT OF BRITISH ANTI-LEWISITE (BAL)

The historical background to the British development of BAL as an antidote for poisonous war gases containing arsenic has been described in some detail.[5-9] This compound has the structure:

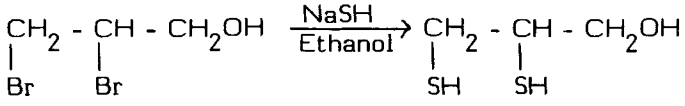


BAL (2,3-dimercapto-1-propanol)

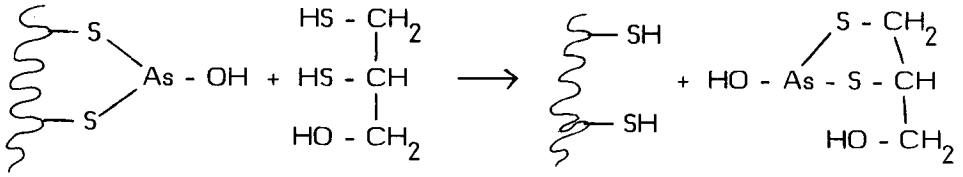
The abbreviation BAL derives from British Anti-Lewisite, the antidote developed by the British for the poison gas Lewisite:



BAL is prepared by the reaction of 2,3-dibromo-1-propanol with an ethanolic solution of NaSH:[135]



The vicinal sulfhydryl groups are the key features which allow this molecule to react with *most* of the metal ions which furnish insoluble sulfides with H_2S. BAL thus is not a chelating agent which reacts specifically only with arsenic. It was selected for large-scale development after examination of a considerable number of structurally related compounds. Its pattern for reaction with an arsenic inactivated enzyme generally is given as

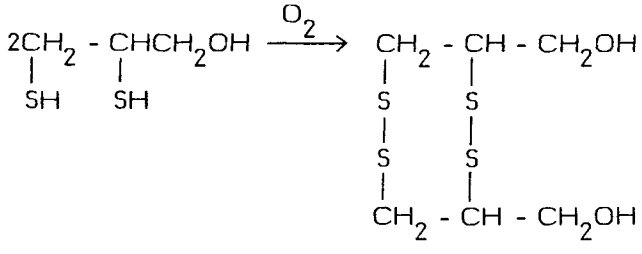


inactivated enzyme | BAL | reactivated enzyme | arsenic-BAL complex

The arsenic-BAL complex then can be excreted in the urine.[199] It is important to remember that at the time BAL first became available, it was almost the *only organic chelating* agent known (and proved in both animal and human studies) to be an effective antidote for *any* kind of metal poisoning. As a result, physicians and research scientists examined its behavior in almost every type of metal intoxication found in humans and animals. This research resulted in a rapid accumulation of data on BAL. BAL was reported to be useful in cases of intoxication by arsenic, mercury, and lead. For many other metals, however, the inherent toxicity of BAL, plus the fact that the complexes it forms with the metal *may* be more toxic than the uncomplexed metal (e.g., the 2:1 complex of BAL with cadmium) has restricted its applications considerably.

A key feature of the arsenic studies was the clear demonstration that arsenic reacts with enzymes to render them inactive. This feature has subsequently been shown to be a very important aspect of the toxicity of almost all toxic heavy-metal ions.

BAL can undergo oxidation via the oxygen in air, *reportedly* to give the corresponding bis-disulfide:



This reaction, which yields other products as well, can be substantially accelerated by the presence of certain metal ions.[108,109]

Because BAL has a *very* limited solubility in water and an unpleasant odor, it must be diluted with peanut oil for administration and its intramuscular injection is a rather painful and unpleasant process.[10–12] The toxicity of BAL is dependent on its purity;

commercial samples may contain some of the much more toxic 1,2,3-propanetrithiol: for pure BAL the LD50 (i.m. or i.p.) in rats is 87 mg/kg; for 1,2,3-propanetrithiol the corresponding value is 19 mg/kg.[216] The use of BAL results in adverse reactions in a fair percentage of the patients; such adverse reactions, which usually pass in an hour or two, include nausea, headache, a burning sensation in the mouth, eyes and throat, crying, salivation, racing heartbeats and other symptoms.[12] Although the complex which BAL forms with arsenic is excreted in the urine, the arsenic content of the brain is increased;[251] similarly, the one it forms with methylmercuric chloride is lipid soluble and can facilitate the transport of methylmercury (but not Hg^{2+}) into the brain.[13] The complex formed with lead is largely excreted in the bile, but it has not been reported to carry lead into the brain. The painful nature of the BAL injections and its own inherent toxicity have mitigated against its use in those disorders where a chelating agent needs to be administered continuously, i.e., those in which copper or iron accumulate because of a hereditary biochemical defect.[14,15] The toxicity of BAL and its metal complexes can also result in the death of a significant number of cells during a course of treatment.

The complexes of BAL are rather inadequately characterized from a chemical viewpoint. The complexes with mercury have been found to be not chelates at all, but polymers in which each Hg^{2+} is bonded to two sulfur atoms in two BAL molecules, no doubt because the normal distribution of bonds about the Hg^{2+} ion is two bonds at an angle of 180°.[16]

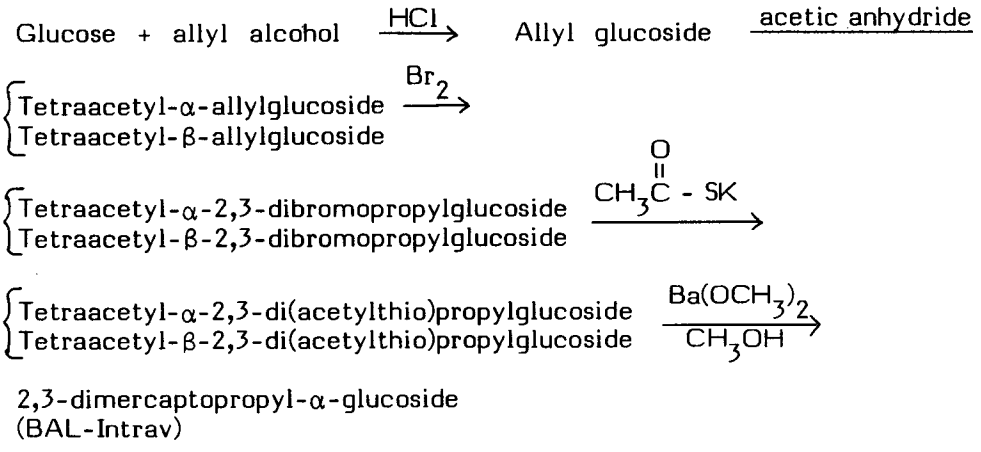
Because of the considerable amount of experience which physicians have acquired with BAL, it is still widely used, though it can be advantageously replaced in almost every case by related compounds of equal efficacy but much reduced toxicity and greater ease of administration (e.g., 2,3-dimercaptosuccinic acid). For example, there is considerable evidence that the widespread use of BAL in the treatment of lead intoxication is not advisable,[219] but it does appear to possess certain advantages when used in combination with $Na_2CaEDTA$.[244]

III. THE WATER SOLUBLE BAL DERIVATIVES

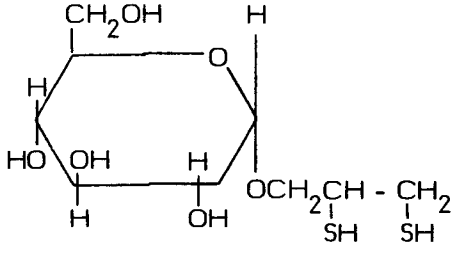
Very soon after the properties of BAL had been determined, it was apparent that compounds containing the two vicinal sulfhydryl groups but also possessing a greater water solubility might be much more useful as antidotes than BAL itself. This has proved to be true, but the high cost and limited availability of such compounds has, in turn, drastically restricted their clinical application. The three compounds which are of interest in this respect are (1) BAL-glucoside, (2) 2,3-dimercaptosuccinic acid, and (3) sodium 2,3-dimercapto-1-propanesulfonate. These are all very soluble in water, less toxic than BAL by 20–40 fold, and can be administered orally.

1. BAL-glucoside (BAL-Intrav)

BAL-glucoside was first prepared in the middle 1940's after the synthesis of BAL. It is synthesized by the following sequence of reactions.[17]



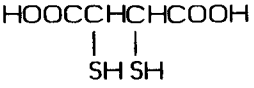
It possesses almost all of the favourable chelating properties of BAL itself. Its structure is:



Its LD50 iv in the rabbit is about 4000 mg/kg compared with a value of 50 mg/kg for BAL. It is an effective antidote for arsenic, lead, and mercury intoxication and forms water soluble complexes with each of these elements.[245] When given soon enough, it can also act as an antidote in acute cadmium intoxication, but it does enhance the cadmium burden of the kidneys.[246] In recent years, the compound has been neglected, largely because of the greater availability of the two compounds listed below.

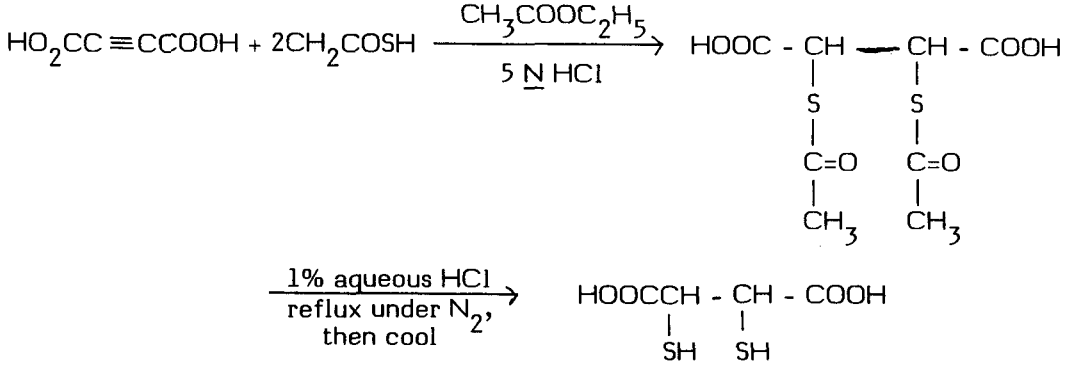
2. 2,3-Dimercaptosuccinic Acid (DMSA)

This compound



was first reported by Owen and Sultanbawa in 1949[18] but its use as a therapeutic chelating agent has occurred more recently, following the publication of an improved synthesis by Friedheim[247] and his demonstration of the effectiveness of this compound in transforming several toxic metals into metal complexes of much reduced toxicity.

The preparation is as follows:



The material produced consists of almost equal amounts of a racemic mixture and the meso form.[111] Pharmacological tests have shown that the D and L forms of the compound have very similar properties in the detoxification of metal ions.[110] Its complexing properties are very similar to those of BAL but, because of the two carboxylate groups, the complexes generally have a much greater water solubility than those of BAL,[248] and a corresponding reduced toxicity. The compound was shown by Friedheim and his co-workers to give an antimony complex of modest toxicity which was effective in the treatment of schistosomiasis.[112] Subsequent studies have shown that this compound is an effective antidote for arsenic, antimony, bismuth, lead, copper and mercury, and can probably be used for other metals with which it forms stable complexes.[19] A comparison of the relative ability of this compound with 15 other chelating agents as antidotes for acute antimony intoxication showed that it was the best antidote by quite a significant margin.[113] In the case of bismuth it is also one of the best antidotes.[114]

This compound has a significant number of advantages over BAL and may well replace it in the future. These advantages include: (1) it can be given orally; (2) it is among the least toxic of the therapeutic chelating agents, with an LD50 for oral administration (to the mouse) *in excess* of 5000 mg/kg;[115] (3) it is rapidly eliminated and does not easily accumulate in the mammalian body. When given orally, about 98% is absorbed from the stomach within two hours[116] while its excretion into the urine subsequent to injection is also rapid, having a half-life of about four hours.[116] The compound is available as a stable white crystalline powder of mild odor and slightly acid taste. Because of the widespread use of its antimony complex in the treatment of schistosomiasis, there is a good deal of information demonstrating its relative safety in humans.[249]

The complexes which DMSA forms with silver, gold and antimony, are stable to the action of H_2S.[117] The reported stability constants for the complexes of DMSA with toxic metals are not numerous, however, and are generally less than 10^{20}. Thus the stability constant for PbDMSA[118] is 3×10^{17}, while that for HgDMSA[119] is 1.7×10^{18}.

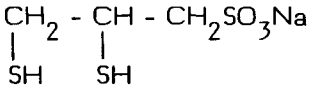
The great stability of the DMSA complexes with the radioactive element technetium have led to their extensive use as scintigraphic agents in the diagnosis of various human disorders, principally kidney malfunctions of various sorts. These

complexes are prepared by the reduction of synthetic pertechnate, $^{99m}TcO_4^-$ in the presence of DMSA.[120]

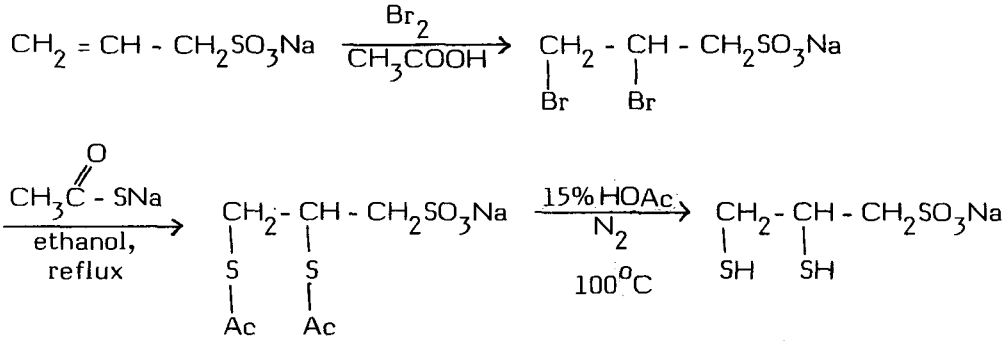
Because of the stability, ease of elimination and low toxicity of the complexes formed by DMSA it seems an excellent candidate for testing in any search for an antidote for a toxic metal ion which forms a very stable sulfide. It gives every indication of being a compound whose use will expand significantly in the future

3. Sodium 2,3-Dimercapto-1-propanesulfonate (Unithiol, Dimaval®, DMPS)

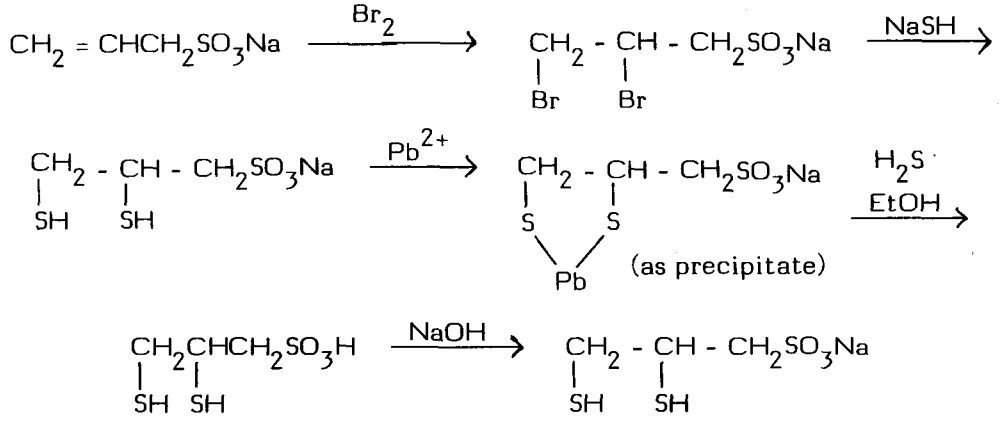
This compound:



was prepared for the first time by Johary and Owen,[20] but its development as a therapeutic chelating agent was largely carried out in the Soviet Union following its independent synthesis by Petrunkin.[21] The sequence of reactions used by Johary and Owen was[20]



Petrunkin's synthetic procedure[21] was as follows:



The material is currently manufactured by E. Heyl and Co. in Berlin using a process that has not been revealed. This process yields an optically inactive product which is available commercially. The name Dimaval is a Heyl trademark.

Like BAL and DMSA, this compound forms complexes with essentially all of the metal ions that give insoluble sulfides with H_2S.

Because of the sulfonate group, DMPS is very soluble in water. It is also much less toxic than BAL, though not so much less as DMSA. There is also a very significant species variation in its LD50 values. In the mouse the LD50 for subcutaneous administration is almost 2000 mg/kg while the analogous values for the cat and the dog are about 300 mg/kg.[121] In mammals the compound is rapidly excreted into the urine subsequent to absorption with about ¾ of it present in the urine 5 hours after injection.[121] It is also subject to fairly rapid oxidation *in vivo* to the mono-and bis-disulfide.[121]

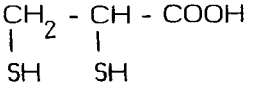
The stability constants of the complexes of DMPS have been determined for a number of toxic metal ions; especially stable complexes have been reported for Hg^{2+}, Ag^{+} and Au^{+}.[122,123]

The compound has found clinical application in the Soviet Union for a number of types of metal poisoning, so clinical and animal data are available for mercury and lead. Animal tests have shown that DMPS facilitates the rapid urinary excretion of arsenic (given as As_2O_3).[124] DMPS also is able to enhance the urinary excretion of both $HgCl_2$[125] and some organomercurials, i.e., methylmercury derivatives (CH_3HgX).[126] In a comparison of DMPS with a large number of other chelating agents it was found to be most effective in removing mercury from the kidneys.[127] While DMPS is an antidote for lead intoxication,[128] it does not seem to possess any obvious advantage over $Na_2CaEDTA$ for this purpose and is about 600 times more expensive.

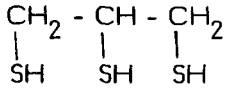
A very extensive comparison of DMPS with DMSA has been made by Aposhian,[19,229,251] who found them significantly superior to BAL in every respect.

IV. OTHER DI- AND POLYTHIOLS

During the last forty years a rather large number of polythiols have been prepared and some of these have been tested as antidotes. Thus a large group of these compounds was screened in the search that led to BAL. Similarly, Petrunkin has reported the preparation of numerous compounds related to DMPS. These compounds, in general, have received relatively little attention since their preparation because they usually have no marked superiority over compounds of this type that are more readily available. It must also be emphasized that compounds of this type which do not possess an ionic group of a sort to guarantee their water solubility are generally compounds of considerable inherent toxicity in their own right. An interesting example of this sort is the structurally promising compound 2,3-dimercaptopropanoic acid:



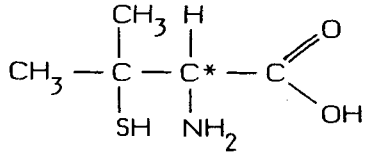
This compound, surprisingly, is *more* toxic than BAL. It does facilitate the excretion of lead and conceivably would be useful for several other types of metal intoxication, were it not for its toxicity. A recent study compared eight different mono-, di-, and trithiols as chelators in chronic cadmium intoxication.[22] Of the compounds examined, only BAL and 1,2,3-propanetrithiol



were reasonably effective in mobilizing cadmium, but 1,2,3-propanetrithiol was found to be the most toxic of the compounds examined, producing a mortality of 30% in rats given 400 μmol/kg; under the same conditions BAL results in no mortality. It must also be remembered that the lipid soluble thiols generally are volatile and possess an extremely disagreeable odor.

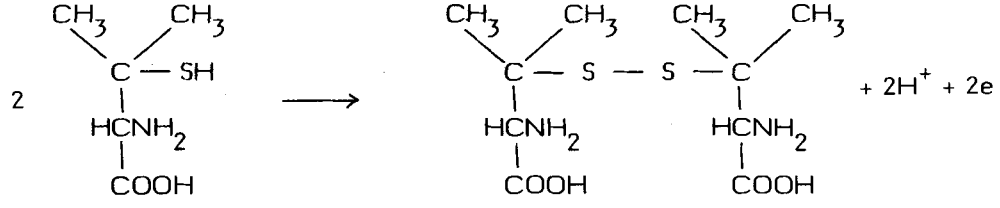
V. D-PENICILLAMINE AND OTHER CYSTEINE DERIVATIVES

The development of D-penicillamine as a therapeutic chelating agent is due to the efforts of Walshe[159] who first found it was present in the urine of a patient with a liver carcinoma who had been given penicillin.[23] After taking some himself to insure its lack of toxicity, he gave some to a patient with Wilson's disease, a hereditary disorder in which copper is accumulated up to a fatal level. He soon established that the oral administration of 1 gram of D-penicillamine led to a 10- to 20-fold increase in the urinary excretion of copper.[24] Subsequently Walshe showed that it could be used to control this disorder, as is described below. The structure of penicillamine is:



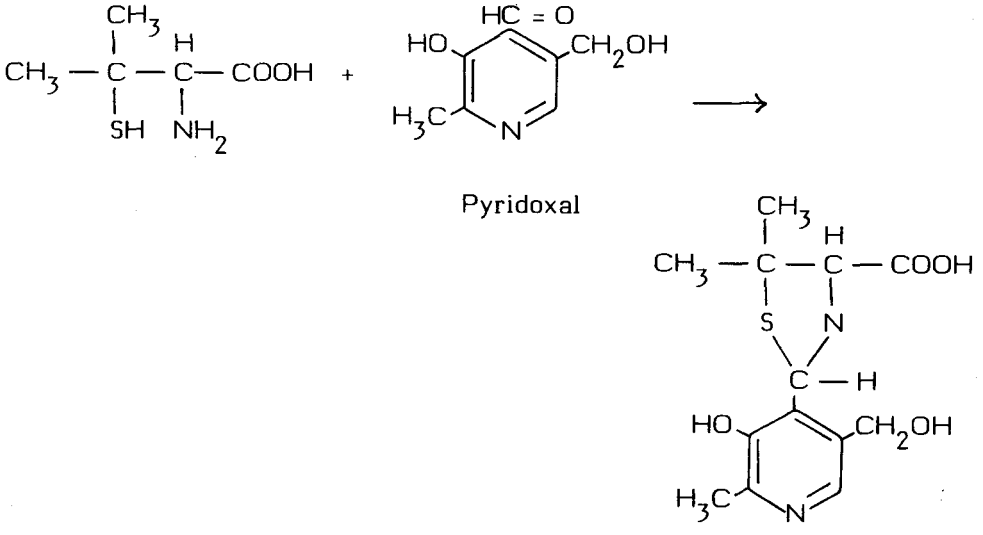
Penicillamine (β,β-dimethylcysteine)

It exists in both a D and an L form by virtue of the chiral carbon. The two methyl groups on the β-carbon atom are very important in making this a generally useful therapeutic chelating agent while cysteine itself is not. Penicillamine can act as a reducing agent by virtue of the formation of its disulfide:



The D-form of penicillamine is obtained commercially by the degradation of penicillin and is used in medicine because it is a compound of appreciably lower

toxicity than the L-form. In mice, the LD50 for intravenously administered D-penicillamine is about 4000 mg/kg.[129] For the L form, the LD50 in mice given the compound intraperitoneally is about 350 mg/kg.[130] L-Penicillamine is known to be an antimetabolite for vitamin B_6 (pyridoxine) by virtue of the reaction with the related aldehyde (pyridoxal) to form a thiazolidine derivative:[160]



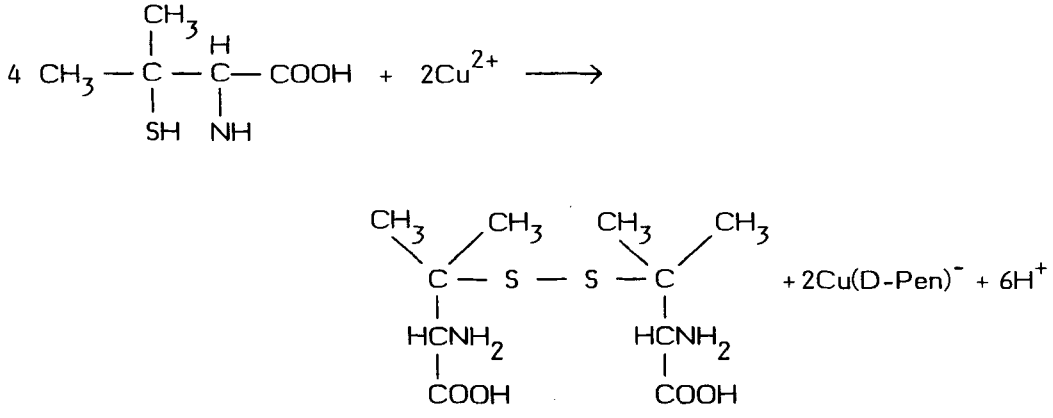
Under certain conditions, the long-term administration of D,L-penicillamine can lead to lesions of the optic nerve, which respond to treatment with pyridoxine.[131] D-Penicillamine has this property to a much lesser extent.

D-Penicillamine possesses S, N and O donor atoms and can use one or more of these at a time to form complexes with many different types of metal ions. Because these donor atoms interact with such a wide variety of cations we find that D-penicillamine forms complexes with just about all the toxic metal ions of interest, although some of these reactions do not occur to an appreciable extent *in vivo*. For example, D-penicillamine will give a reaction with ferric ion in water, but does not dislodge ferric ion from its typical firmly bound sites *in vivo*. In some other cases, the complexes may be formed *in vivo*, but are themselves compounds of great toxicity, e.g., those with cadmium.[161] In this case the administration of D-penicillamine does *not* enhance the urinary excretion of cadmium and, in fact, in rats the cadmium content of the kidney, a very sensitive organ, is increased by the administration of D-penicillamine.[161]

D-Penicillamine is, however, a very useful chelating agent in the detoxification of copper, lead, mercury, nickel, zinc, and antimony, among other metals.[250] It possesses the great advantage over many therapeutic chelating agents that it can be administered orally and usually elicits no adverse effects in the majority of cases. It does have the disadvantage that it may evoke an allergic response in individuals who are allergic to penicillin and this has prevented its blanket recommendation for use in any kind of chronic metal intoxication.

D-Penicillamine is of special importance in the treatment of hepatolenticular degeneration (Wilson's disease).[132] This disorder is due to a hereditary biochemical

defect leading to the accumulation of copper in the liver, brain, and kidney as well as the other organs. It causes a variety of neurological problems and ultimately death as the level of accumulated copper steadily rises. D-Penicillamine, given orally at a level of about 1 gram per day, leads to a sufficiently great increase in the urinary excretion of copper to allow this disorder to be controlled over long periods of time (25 years).[159] The long-term administration of such a chelating agent can be expected to enhance the urinary excretion of some other metal ions. In animals, the administration of D-penicillamine enhances the urinary excretion of the essential ions copper, zinc, and to a lesser extent calcium as well as toxic metal ions such as mercury, arsenic, lead and thallium. The excretion of many other trace elements is little affected.[162] The excretion of zinc is counterbalanced by the increased absorption of zinc in the gastrointestinal tract when D-penicillamine is given orally.[163] The interaction of D-penicillamine with copper proceeds both via complexation and via reduction as shown by the equation,



where the final copper is univalent and complexed with D-penicillamine.[160] It is necessary to note that the above reduction of Cu^{2+} is dependent on the concentration and the media; in fact, metal complexes of penicillamine are known which are polymeric species because the $-S^-$ species can form coordinate bonds to two different metal ions. With copper, for example, the complex anion $[Cu(I)_8Cu(II)_6(pen)_{12}Cl]^{5-}$ has been found in the solid state.[164] Because the S donor atom can coordinate to *two* Cu^+ ions, polymeric species in which D-penicillamine is coordinated only through the sulfur atom may be found under acidic conditions.[165] It has been shown that Cu(II) in the presence of glycylglycine or histidine and D-penicillamine will form a mixed complex with Cu^{2+} in which reduction does not occur.[166] The nature of copper transport in Wilson's disease has been reviewed,[167] where the conclusion is drawn that reduction may be unimportant.

D-Penicillamine forms a very stable 1 : 1 complex with Pb^{2+}.[168] The solid complex Pb(pen) has the lead in the center of a distorted pentagonal bipyramid bonded to six donor atoms, the O, N and S of one D-penicillamine and an O and two S atoms from other D-penicillamines bound to other Pb^{2+} ions.[169] The stability constants of the lead(II)-D-penicillamine complexes have been determined by several sets of

investigators.[230,231] At physiological pH values, the Pb-D-penicillamine 1:1 complex is formed and the equilibrium constant for its formation (stability constant) is close to 10^{13}. The complexes of penicillamine and of cysteine with metals have been reviewed.[170] Ions and their complexes of interest to the toxicologist include: Hg^{2+} [$Hg(cystH)_2$ with bonding only through the sulfur atoms], Cd^{2+} [$Cd(pen)_2$ in which each Cd^{2+} is surrounded by 2-S, 3-O and 1-N atoms] and CH_3Hg^+, which forms a complex through a single sulfur atom of the D-penicillamine.[170]

D-Penicillamine is very effective in the treatment of chronic lead intoxication.[133] Urinary excretion of lead is increased about 10-fold and blood lead levels decrease significantly. The use of oral D-penicillamine therapy is much more convenient than the usual injections of $Na_2CaEDTA$ and/or BAL used to enhance the excretion of lead. The levels of D-penicillamine used clinically are much lower than those which produce toxic effects in animal studies. These animal studies show that D-penicillamine has a much greater effect in reducing endogenous copper levels than the levels of the other essential ions with which D-penicillamine can also form complexes, e.g., zinc and iron.[136,171] Such studies indicate that the use of D-penicillamine in lead intoxication can be expected to lead to enhanced excretions of copper, zinc and iron.

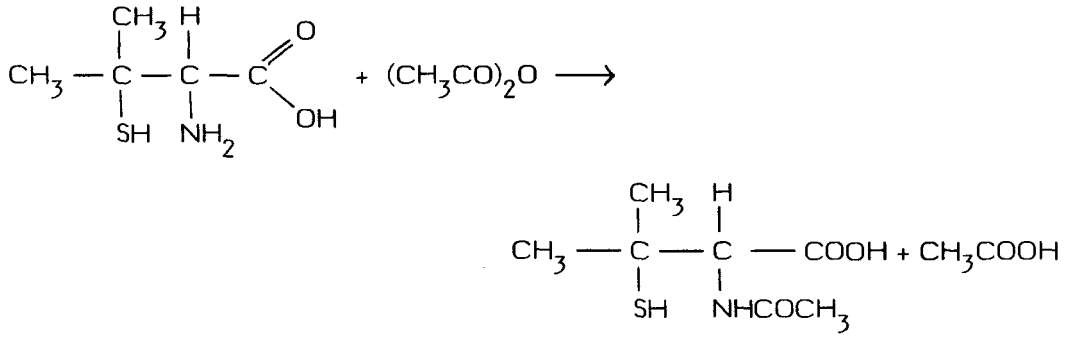
D-Penicillamine is an antidote for acute $HgCl_2$ intoxication[172,173] and also can enhance the excretion of some organic forms of mercury.[174]

Because D-penicillamine is used in the treatment of several other disorders (e.g., rheumatoid arthritis and cystinuria) there is a great deal more information available on its pharmacological and adverse effects than is the case with most therapeutic chelating agents.[175] The adverse effects are numerous and may become very serious. The include[176] febrile reactions, nausea, anorexia, vomiting, loss of taste, rashes, thrombocytopenia, aplastic anemia, mouth ulcers, proteinuria, nephrotic syndrome, myasthenia gravis, systemic lupus erythematosus and cholestatic jaundice. These effects do not always occur, since there are individuals with Wilson's disease who have been treated with D-penicillamine for years without serious side effects, but they are somewhat more frequent, it would seem, in individuals being treated for rheumatoid arthritis. The loss of the sense of taste upon repeated administration of D-penicillamine is due to the loss of copper needed in the taste organs and is reversed by the administration of copper.[177]

The metabolism and pharmacology of D-penicillamine has been studied in some detail in both rats[178] and man.[179,180] Following oral administration, D-penicillamine is rapidly absorbed to the extent of 50–60% with the balance excreted in the feces. Of the amount absorbed, a considerable fraction is bound to serum and tissue proteins and remains bound after 24 hours. Of the amount excreted in the urine (approximately 40%), the relative amount of the different metabolites varies with the disease of the individual. Major metabolites in the urine include penicillamine disulfide and the mixed cysteine penicillamine disulfide as well as norleucine, S-methylpenicillamine, glycine, alanine, cystine and homocysteine-penicillamine disulfide.[179] Less than 1% is metabolized to CO_2.[25]

In vitro, penicillamine can penetrate cell membranes only slowly and this is stopped by the presence of copper or gold ions.[181] The ability to penetrate cell membranes can be manipulated via structural modification (see below).

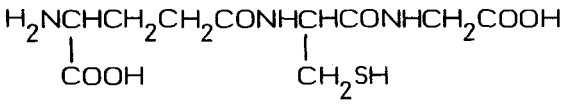
N-Acetyl-D,L-penicillamine. This compound is prepared by the acetylation of D,L-penicillamine:



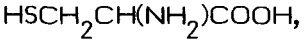
The acetylation of the nitrogen causes some significant changes in the properties of the compound. It is no longer a vitamin B_6 antagonist nor does it cause an enhancement in the urinary excretion of copper.[136] The acetylated nitrogen is no longer a very effective donor atom towards metal ions. The compound can move across cellular membranes more readily than the parent compound.[137] Its ability to act as an antidote for acute copper intoxication is not greatly altered.[182]

It was first shown to be an effective antidote for mercuric chloride intoxication by Aposhian and Aposhian in 1959.[158] N-Acetyl-D,L-penicillamine is extremely effective in enhancing the excretion of mercury, given as methylmercuric chloride, from both the brain and the whole body of mice.[137] It is also capable of removing CH_3Hg^+ from both the adult and the fetal rat[158] and similar results were obtained with adult Macaca monkeys. It is a compound which is less toxic than D-penicillamine and can be given to animals over an extended period of time with far fewer side effects. In mice it has been given at a level of 27 mmol/kg orally for four days without giving rise to any toxic symptoms.[250]

Glutathione, Cysteine, and Other Cysteine Derivatives Glutathione, which is a tripeptide containing a cysteine residue, N-(N-L-γ-glutamyl-L-cysteinyl)glycine



and cysteine, which has the structure



are both important thiols *in vivo*. Glutathione is the most common low-molecular weight thiol compound in cells. Because of the presence of the thiol group glutathione

is important in the interaction of living cells with toxic heavy metals which bond to thiols. These include mercury, lead, cadmium, arsenic, antimony, bismuth, zinc, copper and selenium among others. Serum glutathione is not able to penetrate cellular membranes as such,[237] and for this reason, the use of glutathione, per se, as a therapeutic chelating agent has not been common.

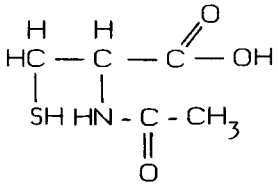
Glutathione was shown to inhibit the action of arsenoxide (R-As=O) on trypanosomes *in vitro* and *in vivo* (rats) as early as 1923.[238] Subsequent studies[239,240] showed that glutathione was also an antidote for otherwise lethal doses of arsenoxide in the rat, that cysteine was less effective than glutathione, and that the imflammatory reactions typically caused by arsenious acid could also be prevented by glutathione. Subsequently the fact that arsenic can provide protection against the toxicity of selenium under some conditions led to a study to see if glutathione could also furnish such protection. It was found that if glutathione (at a mole ratio of 10:1) is injected into rats hours prior to the injection of sodium selenite at 3.5 mg/kg, the survival rate of the rats was increased dramatically (from ~10 to 80%).[241] The interaction of selenium and glutathione has also been studied under other conditions.[186]

The biliary excretion of CH_3Hg^+ takes place with much of this species present in the form of its glutathione complex [183] and the same is probably true of zinc[184] and cadmium.[185] Glutathione also interacts with organometallic species after their administration.[187]

The close connection between hepatic glutathione levels and the hepatotoxicity induced by the administration of cadmium has been clearly demonstrated.[242] Pretreatment to reduce hepatic levels of glutathione significantly increases the toxicity of cadmium, while pretreatment to increase such levels decreases cadmium toxicity. The effect of various metal ions on cellular glutathione metabolism has been reviewed.[243]

A number of compounds structurally related to penicillamine have been examined for their effectiveness as detoxicants for copper and mercury.[138] Cysteine and β-methylcysteine are without effect on the urinary excretion of copper in Wilson's disease, while replacement of a methyl by an ethyl group in D-penicillamine, or acetylation of its nitrogen gives compounds which are effective against the lethal action of mercuric chloride in the rat.

N-Acetyl-D-cysteine



is widely used as a mucolytic agent so it is quite readily available. It has been successfully used in the treatment of gold intoxication resulting from the treatment of rheumatoid arthritis with gold salts.[139]

VI. N-(2-MERCAPTOPROPIONYL)GLYCINE (THIOLA)

This compound has the structure:

$$HSCH(CH_3)CONHCH_2COOH$$

Several preparations have been reported for it; the first[140] is:

$$H_2NCH_2COOH + C_6H_5CH_2SCH(CH_3)COCl \xrightarrow[2.\ H^+]{1.\ NaOH,\ 3\text{-}5^oC} C_6H_5CH_2SCH(CH_3)CONHCH_2COOH \xrightarrow[NH_3]{Na,\ in} C_6H_5CH_3 + CH_3CH(SH)CONHCH_2COOH$$

Other preparations have also been reported.[141] The pure compound is a white solid, m.p. 95–7 °C, and quite soluble in water. This compound has also been used in the treatment of hepatitis, cirrhosis, the toxemias of pregnancy and cysteinuria.[142,143] This compound has an LD50 of 2100 mg/kg when given intravenously to the mouse.[144] The LD50 in rabbits is 1200 mg/kg (i.v.).[27] The compound has an antidotal action towards $HgCl_2$ and sodium arsenite. When given at high levels it can enhance the urinary excretion of copper, but at a level of 50 μmole/kg it is not so effective as D-penicillamine.[145]

It has been used clinically in the treatment of lead poisoning.[280] Among the most interesting of the studies carried out on this compound are those in which it has been shown to be effective in offsetting toxicity due to various types of organomercury compounds. When given orally at a level of 600 mg/kg to individuals with mercury poisoning, it increased the urinary excretion 3–6 fold.[30] Treatment of animals which had been given radioactive ethylmercuric chloride showed that this compound was capable of reducing the mercury content of all the organs after three days.[31] In a study which compared the action of this compound on a series of organomercury compounds, it was found to give the greatest enhancement of excretion with CH_3HgCl and a reduced effect with C_6H_5HgOAc and $HgCl_2$.[32] When given promptly after methylmercuric chloride, the teratogenic and fetotoxic effects usually found can be prevented.[146]

Although the syntheses of analogs with amino acids other than glycine would seem straightforward with some of the reactions used to prepare "thiola", these seem not to have been investigated.

VII. DITHIOCARBAMATES

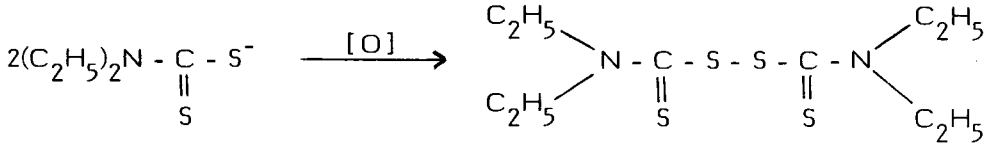
Dithiocarbamates were prepared as early as 1850, but their exploitation as chelating agents began when their unusual ability to bond firmly to metal ions was reported by

Delepine[188] who subsequently initiated their use in analytical chemistry.[189] This led to the extensive use of diethyldithiocarbamate:

$$(C_2H_5)_2NC(S)S^-, Na^+$$

which is now commercially available as the trihydrate. Subsequently the dithiocarbamates have been used in industry;[190] their metal complexes are widely used as fungicides,[190] and in analytical chemistry.[189,191,192,232] For the majority of such purposes it is desirable to prepare metal complexes which are insoluble in water, but soluble in organic solvents. As a result of this, there is an enormous amount of information on dithiocarbamates and their metal complexes in which the substituents on the nitrogen atom are manipulated to achieve these ends, i.e., the substituents are organic groups (aliphatic, heterocyclic, aromatic, etc.) of very low polarity. As a consequence, the metal complexes themselves are frequently fat and lipid soluble, a property which has certain disadvantages for *in vivo* studies. One point which has become quite apparent from recent studies is that changes in the substituents on the nitrogen atom can have very significant effects on the organ distribution of the metal complexes which are formed. These effects are responsible for the fact that some of the dithiocarbamates of greatest promise as metal antidotes are quite different from the ones most useful in analytical chemistry.

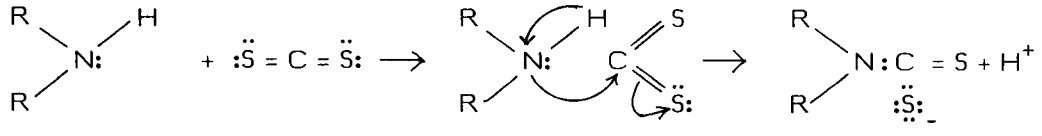
The oxidation of diethyldithiocarbamate leads to disulfiram:



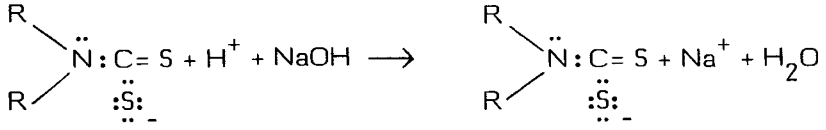
Disulfiram

a compound which causes a toxic reaction if alcohol is taken after its administration.[233] Its subsequent use in the treatment of alcoholism has led to extensive studies on its metabolism.[234–236] The first step in the metabolism of disulfiram is its reduction back to the diethyldithiocarbamate ion, which is a rapid process. Subsequently much of the ion is conjugated with glucuronic acid, while smaller amounts undergo non-enzymatic degradation, methylation, or oxidation. As a result of these studies, the metabolic disposition of dithiocarbamate is known in some detail.

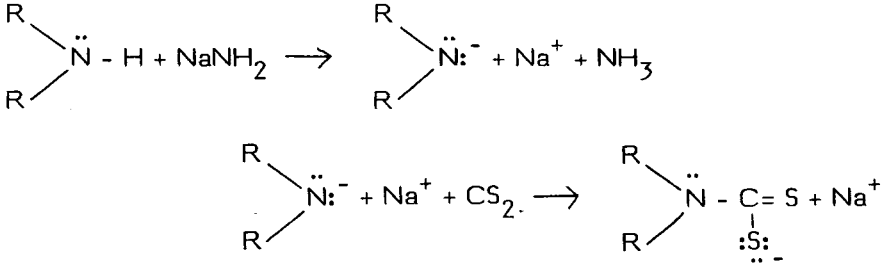
Because of its advantageous pharmacological properties, the sodium ion is the one preferred for use in dithiocarbamates that are to be administered internally. The preparation of the sodium salts can be effected in a number of ways, depending on the basicity of the nitrogen atom involved. The reaction proceeds via the attack of the electrophilic CS_2 molecule on the nucleophilic nitrogen:



is facilitated by the presence of a base to remove the proton, i.e.,

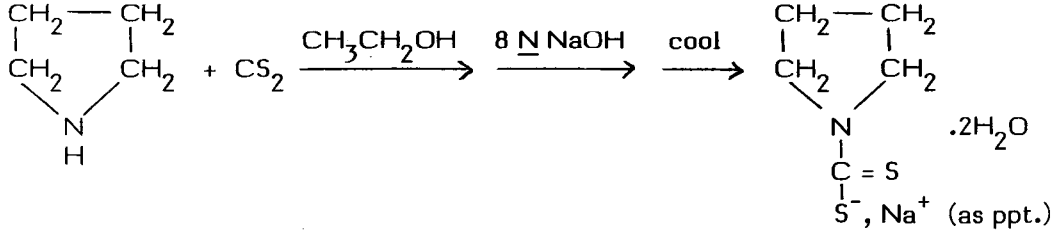


Where the amine is weakly basic, the reaction can be facilitated by use of a strong base in a non-aqueous medium, e.g.



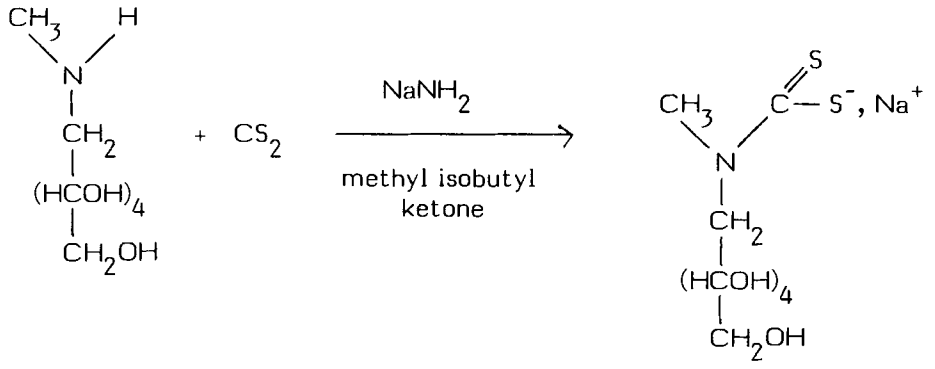
In many cases ethanol can be used as a solvent. While dithiocarbamates can be prepared from both NH_3 and primary amines, they have been little examined as therapeutic chelating agents because of their instability at physiological pH values.

Most of the preparative procedures used trace back to the studies of Delepine, but later studies often have given simplified directions for the preparations of the solid soldium salts; e.g., Gleu and Schwab[193] describe the preparation of the dithiocarbamates derived from dimethylamine, diethylamine, piperidine, pyrrolidine, piperazine, morpholine and thiazane via the process:



Klopping and van der Kerk[194] describe the preparation of a large number of dithiocarbamates of primary and secondary amines via reaction in the presence of water followed by evaporation in vacuo.

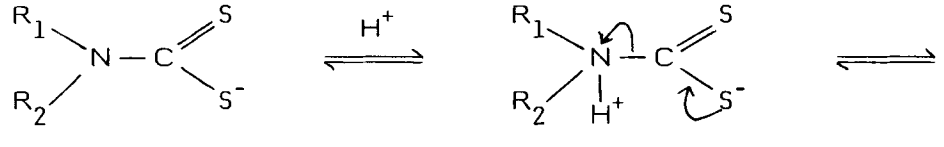
A different procedure was used by Bode and his co-workers[195] to prepare the sodium salt of the N-methyl-D-glucamine compound. Here methyl isobutyl ketone was used as the solvent and, after the addition of the N-methyl-D-glucamine and CS_2, sodium amide was added in small portions. The crude product precipitates when the mixture is cooled and subsequently the impure material is purified via recrystallization from water to which methanol is added.

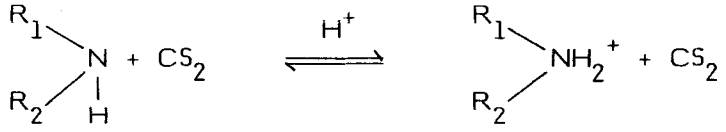


This procedure is useful with a wide variety of N-H structures in which the nitrogen atom is only weakly basic.

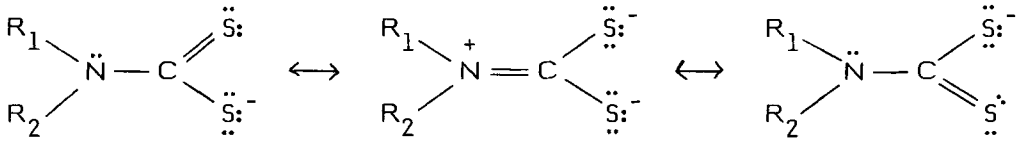
Where more than one amino group is available and reactive towards CS_2, the usual product has the dithiocarbamate derived from the *less* basic amine while the more basic amine is protonated and is the cation of the zwitterion if no added base is present in the reaction mixture.[196,197] Such reactions with identical amino groups also lead to a zwitterion in similar reaction conditions, though the bis dithiocarbamate generally can be prepared by the addition of two moles of strong base, such as NaOH.[198]

Dithiocarbamates generally are unstable in acidic media and decompose as follows.





The dithiocarbamates form complexes with most of the ions that give insoluble sulfides with H_2S, and the inorganic chemistry of these complexes has been reviewed.[189,191,200–202] The dithiocarbamate ion is planar because of the partial double bond between the carbon and the nitrogen atoms:



The result is that a transition metal ion may be symmetrically bonded to the dithiocarbamate ion and lie in this same plane.[202] For complexes of the main-group elements the bonding is generally asymmetric.[202]

The biological properties of dithiocarbamates, which have been extensively studied,[217] often are related to their ability to form quite stable complexes with essential metal ions, such as copper and zinc. Such studies on dithiocarbamates frequently have suffered from the fact that the most readily available compound of this class is sodium diethyldithiocarbamate, a compound produced primarily for use in analytical chemistry. In analytical chemistry it is used mostly to form metal chelate complexes that can be extracted into an immiscible organic solvent, such as chloroform. These extractions can greatly facilitate the separation of various elements.[38] Because this compound forms electrically neutral chelate complexes (which are either non-polar or of very low polarity) with most divalent and trivalent ions of interest to the toxicologist, the *in vivo* distribution of these complexes in the various organs tends to be similar to that of non-polar organic compounds. Most importantly, such complexes can cross the blood/brain barrier and increase the metal content of the brain as well as other organs. This has been demonstrated for copper,[33–35] zinc,[34,35] methylmercury,[36] polonium,[49] thallium,[47] mercury and lead[211] and cadmium.[212] The useful and attractive properties of the dithiocarbamate group itself, thus have often been masked by the lipophilicity of the groups generally attached to it and the fact that such groups also strongly favor the formation of lipophilic metal chelate complexes. This behavior, which is related to the polarity of the substituent groups present on the nitrogen[106] has mitigated against the use of sodium diethyldithiocarbamate in cases of metal intoxication where any other chelating agent has shown itself useful. The dithiocarbamate group actually is capable of forming stable complexes with the great majority of the metal ions in the central portion of the periodic table,[38] though some of these complexes are not formed at physiologically attainable pH values.

The use of dithiocarbamates as therapeutic chelating agents stems from the observations of Sunderman and his co-workers that sodium diethyldithiocarbamate is an effective antidote for nickel carbonyl ($Ni(CO)_4$) poisoning in animals[203] and humans.[204,205] Nickel carbonyl is produced in one of the commercial processes for the purification of nickel. It is a low-boiling liquid and is very toxic; industrial intoxication was noted as early as 1902. West and Sunderman[203] examined the relative efficacy of fourteen different dithiocarbamates as antidotes for nickel carbonyl intoxication in rats. On the basis of its high efficacy and low inherent toxicity, sodium diethyldithiocarbamate appeared to be the most promising antidote. It acts probably indirectly, by forming a very stable complex with nickel and in enhancing the excretion of nickel. Subsequently this compound was used clinically and proved its worth.[204] In the years since its introduction it has been used successfully in the treatment of hundreds of cases of nickel carbonyl intoxication. Sunderman was able to show that sodium diethyldithiocarbamate led to an enhancement in the urinary and fecal excretion of nickel in rats given $Ni(CO)_4$ and in the urine of humans (the feces were not analyzed) with $Ni(CO)_4$ intoxication.[206] In this same report are data showing that sodium diethyldithiocarbamate in an individual with Wilson's disease can lead to a large increase in the excretion of nickel (but not copper). Suggested dosage schedules for the oral administration of sodium diethyldithiocarbamate also have been given by Sunderman.[207] Sodium diethyldithiocarbamate also is capable of reducing the incidence of tumors in rats which have been treated with Ni_3S_2, nickel subsulfide.[208] In

subsequent studies, disulfuram and D-penicillamine have been found to have an antidotal efficacy comparable to that of sodium diethyldithiocarbamate at lower levels of nickel carbonyl exposure in rats.[209] Sodium diethyldithiocarbamate is effective when given orally, presumably because its rate of absorption is greater than its rate of decomposition.

The demonstration that sodium diethyldithiocarbamate is an effective antidote for acute cadmium intoxication in animals is due to Gale and his co-workers[39] who also showed that it was effective in mobilizing aged deposits.[40,218] The efficacy of related compounds and their use in allowing the mobilization of aged cadmium deposits was demonstrated by Jones and his co-workers,[106,220–222] who showed that sodium di(hydroxyethyl)dithiocarbamate and related polar structures were as effective as the diethyl compound but did not lead to an increase in the cadmium levels of the brain. These results have been confirmed and extended to a variety of analogous compounds, and it has been shown that most of these compounds enhance the fecal excretion of cadmium.[223] Because aged cadmium deposits are primarily held intracellularly tied up in metallothionein, the special activity of the dithiocarbamates with cadmium implies that the active compounds are capable of passing through cellular membranes, via some mechanism or other.

The unusual chelating ability of diethyldithiocarbamate also can offset the toxicity of cis $[PtCl_2(NH_3)_2]$ (cis-platinum), a compound used in the treatment of cancer. The ability of diethyldithiocarbamate to inhibit the nephrotoxicity of cis-platinum was first reported by Borch and Pleasants.[224] Subsequently it was shown that when the dose of diethyldithiocarbamate was low enough, the nephrotoxicity could be reduced without interfering with the anti-cancer effect of cis-platinum.[225] These results have been confirmed and extended to analogous situations in rat models.[226,227] While the reduction in nephrotoxicity is significant however, the nephrotoxicity is not eliminated.[228]

In conclusion, it seems reasonable to expect that the dithiocarbamates will slowly assume a growing importance as therapetuic chelating agents as their unique chelating properties are more widely exploited.

VIII. XANTHATES

The xanthates have been examined in a relatively limited number of cases. Their facile decomposition has mitigated against their wider use, as has the limited commercial availability of their sodium salts in the solid state. They are, however, easily prepared via the reaction of alkoxides with carbon disulfide, e.g.,

$$NaOC_2H_5 + CS_2 \longrightarrow NaSC(=S)OC_2H_5$$

Like many related sulfur-bearing functional groups, the xanthate group is an excellent donor group toward almost all metal ions that form insoluble sulfides. A comparison of potassium N,N-dimethyl-β-aminoethylxanthate, potassium N,N-diethyl-β-aminoethylxanthate, and potassium ethyl xanthate as antidotes in experimental

cadmium and copper intoxication showed that the first two of these compounds are effective antidotes for copper sulfate intoxication.[54] In the case of cadmium chloride, the data show an antidotal effect for sodium ethyl xanthate for female rats when given 5 or 45 minutes after the cadmium chloride. No such effect was found for male rats. The other xanthogenates had no effect on the course of cadmium intoxication. In another study,[55] it was found that potassium or sodium ethylxanthate increased the toxicity of lead acetate. In such cases, the origin of an increased toxicity often lies in the fact that the metal complex formed can gain access to more sensitive organs than can the original metal salt.

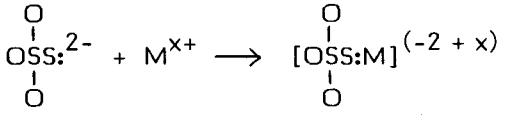
IX. SODIUM THIOSULFATE, $Na_2S_2O_3 \cdot 5H_2O$

The metal complexing abilities of the thiosulfate ion, $S_2O_3^{2-}$, have been known for well over a century. It forms complexes with most of the metal ions which form insoluble sulfides, especially with some of that group of metals typically known as the toxic heavy metals, e.g., Hg^{2+}. These complexes, however, are not all particularly stable under physiological conditions. The stability constants of the complexes $M(S_2O_3)^{\pm\times}$, insofar as these have been measured, are with a few important exceptions quite small. The log K for the formation of $Hg(S_2O_3)_2^{2-}$ is 29.93, but this is by far the most stable complex for which such data are available. Corresponding values for some other complexes are[56]

Complex:	$Ag(S_2O_3)^-$	$Cu(S_2O_3)^-$	$CH_3HgS_2O_3^-$	$Pb(S_2O_3)_2^{2-}$
log K	8.82	10.35	10.91	2.41

Other complexes for which stability constants are not available, but which seem to be very stable, are $Au(S_2O_3)_2^{3-}$ and related complexes of the platinum metals. The information on stability constants fits in rather well with the data reported on the use of thiosulfate as a heavy-metal antidote.

Thiosulfate apparently first was suggested as an antidote for toxic heavy metals by Sabbatani in 1904.[57] He reported it to be effective in the cases of silver, copper and mercury poisoning, but ineffective in the case of lead. Sodium thiosulfate itself is a compound of very modest toxicity. The thiosulfate ion forms complexes with heavy metals via the process:



The commonly used form $Na_2S_2O_3 \cdot 5H_2O$ is available in a state of high purity and is widely used in analytical chemistry. It can be given intravenously to humans, or orally. The lowest dose at which toxic symptoms arise for orally administered $Na_2S_2O_3 \cdot 5H_2O$ is 300 mg/kg in man.[58] Individuals taking 3 g orally per day exhibited

various degrees of cyanosis after a week or two; one individual was reported to have taken a dose of this size daily for a period of two months, with the major effect being a degree of cyanosis.[58] A dose of 1500 mg/kg given intravenously to dogs at a constant rate over a 30-minute period is well tolerated.[74] When given orally, sodium thiosulfate is expected to undergo extensive decomposition in the stomach, because of the acidity there.

Interest in the use of sodium thiosulfate as an antidote for heavy metal intoxication greatly increased after the report by Ravaut in 1920, that it was effective in the clinical treatment of arsenical dermatitis,[59] a condition which occasionally accompanied the then common usage of organic arsenic compounds in medicine. Following this, there were a number of other reports confirming this finding and extending it to other metals[60–66] including mercury, lead, and bismuth. The subsequent literature is not in accord with all of these claims. In animal studies, thiosulfate was found *not* to be an antidote for arsenic[67,69] or lead.[68] From the clinical reports, it must be concluded that thiosulfate is an antidote for organoarsenicals when these are given in amounts typical of *clinical* doses. It is not an effective antidote for large amounts of arsenite. In the case of lead, thiosulfate would appear *not* to be an antidote, a conclusion completely in accord with the very low stability constant of the $Pb^{2+}-S_2O_3^{2-}$ complexes. Sodium thiosulfate also has been reported to *decrease* the toxicity of selenate (but not so much as sulfate does), while it can increase the toxicity of selenite.[75]

In recent years, thiosulfate has been introduced to control the nephrotoxicity of cis$[Pt(NH_3)_2Cl_2]$ used in cancer treatment.[70–73] It is possible to use a combined treatment which is much more effective than cis$[Pt(NH_3)_2Cl_2]$ alone by giving the cis$[Pt(NH_3)_2Cl_2]$ intraperitoneally and the sodium thiosulfate intravenously. This combination prevents the kidney damage due to cis$[Pt(NH_3)_2Cl_2]$ but allows the intraperitoneal concentration of cis$[Pt(NH_3)_2Cl_2]$ to be high while its serum concentration is low.[73]

There seems good reason to believe that sodium thiosulfate may be a useful compound for controlling the nephrotoxicity of medically useful compounds of gold and the platinum metals as well as mercury. It has the interesting property of being able to penetrate the membrane of the human erythrocyte,[76] a property also possessed by the thiocyanate ions.[77] Its distribution volume in the human body is slightly greater than that of the extracellular fluid compartment as measured by the volume of distribution of insulin.[78]

X. MISCELLANEOUS COMPOUNDS WITH SULFUR DONOR ATOMS

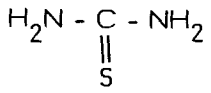
Because the sulfhydryl group in *any* compound will react with a large number of metal ions:

$$R\text{-}SH + M^{x+} \longrightarrow RS{:}M^{+x-1} + H^+,$$

the number of such compounds that have been reported to exert an influence on the toxicity of metal ions is quite large. Many of these have been used only once or twice, but there are some which have been more widely investigated. These include

thiourea, spironolactone, and a large number of compounds containing the reactive -SH group.

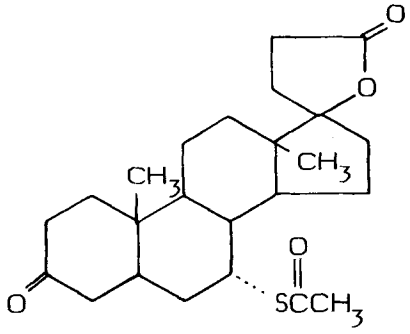
1. Thiourea



The coordination preferences of thiourea are reminiscent of those of thiosulfate; very stable complexes are formed with Cu^+, Ag^+, Au(I) and the platinum metals; weak complexes are formed with a number of other cations. Thiourea has a goitrogenic effect and is carcinogenic, so there has been little reason to examine its antidotal properties in recent years, though it has been shown capable of reversing cis-platinum induced cross linkage of DNA and restoring the biological activity of the DNA.[79]

2. Spironolactone

Spironolactone was first shown to influence the distribution of mercury by Selye in 1970[80] and to be capable of preventing mercury poisoning in animals under certain conditions. It was subsequently shown to increase the biliary and fecal excretion of mercury[81,82] and of copper.[83] Pretreatment of rats with spironolactone has also been shown to reduce the effects of cadmium on the key gluconeogenic enzymes in rat kidney and liver.[84] The structure of spironolactone is

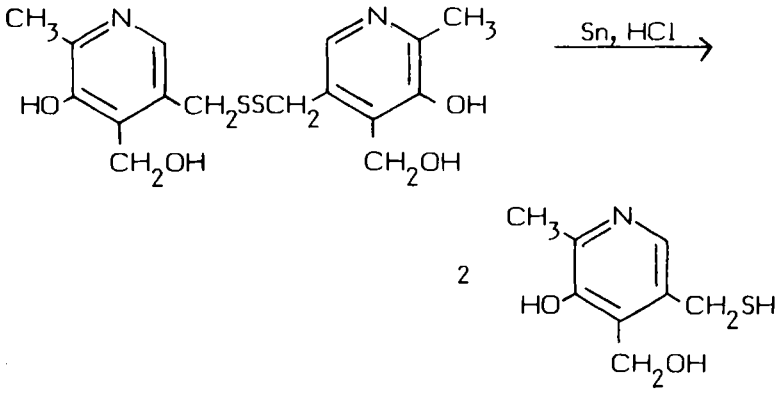


Spironolactone causes mercury to be more widely distributed in the mammalian body, but by doing so it reduces the concentration in the kidney—this feature probably is responsible for its protective action.[85]

In the case of CH_3HgCl, the co-administration of sulfhydryl-containing compounds such as L-cysteine can lead to increasing organ concentrations of CH_3Hg^+[86] Methylmercury chloride, and possibly, many other organo-metallic compounds, pass easily through cell membranes and rapidly reach sensitive sites in the brain, liver, kidneys and other organs. In a study on $(C_2H_5)_3PbCl$, it was shown that cysteamineacetic acid ($HSCH_2CH_2NHCH_2COOH$), β-mercaptoethylguanidine and β-mercaptoethylamine were all capable of reducing the mortality in a group of mice that had received a normally fatal dose of $(C_2H_5)_3PbCl$.[87]

3. *Pyridoxine-5-thiol*

This compound has been reported to be effective in eliminating CH_3Hg^+ from the brain.[88] It is prepared by the reduction of the disulfide:



It was reported to cause no histological changes in the livers of rats receiving a total of 800 μmoles (150 mg) over a period of 10 days.

XI. POLYMERS WITH SULFUR-CONTAINING DONOR GROUPS

The use of an insoluble polymeric material containing sulfhydryl groups to absorb a toxic metal from the gastrointestinal tract was reported first by Takahashi and Hirayama[89] in 1971. These workers reduced the -S-S- groups in powdered hair to -SH groups and found that the resulting material was able to absorb mercury compounds.

Subsequently several other groups of investigators prepared and examined a number of purely synthetic polymers designed with the same goal in mind: the absorption of one or more toxic metal ions from the gastrointestinal tract via the formation of stable coordinate bonds to some sulfur-containing functional group incorporated in the polymer. Clarkson and his co-workers used a modified polystyrene containing -SH groups in much the same way as Takahashi and Hirayama.[90] Aaseth and his collaborators prepared mercaptodextran[91] and showed that it could be given to mice via intravenous transfusion to antagonize lethal doses of $HgCl_2$[92] if given immediately after the $HgCl_2$. The preparation of a mercaptodextran via the reaction of dextran with N-acetylhomocysteine gave a polymer which could be incorporated into the food of animals and which reduced the biological half-life of CH_3HgCl from 11.6 days to 5.9 days.[93] The polymer apparently released N-acetylhomocysteine and this, in turn, enhanced the urinary excretion of mercury. Similar results were obtained by the injection of N-acetylhomocysteine itself.

Jones and his co-workers prepared polymers containing sulfide and sulfhydryl groups and examined their behavior.[94–98] These polymers absorbed CH_3Hg^+, Hg^{2+}, Pb^{2+}, Cd^{2+}, and Cu^{2+}, but their capacity for absorbing such ions was quite limited because of the relatively small surface-to-volume ratios of the polymers. Subsequently

these polymers were prepared in the form of microspheres by Margel[99] and Margel and Hirsch[100] and were shown to be capable of removing mercury compounds from poisoned plasma.

The adoption of such polymers for actual clinical use would seem to be dependent on the development of a polymer that could absorb a very wide variety of toxic metals. Such a polymer probably would need to have N and O donor sites incorporated as well as donor sites based on S. The polymer then could be administered *orally* to prevent the absorption of most toxic metals from the gastrointestinal tract and probably would be quite useful clinically.

XII. MISCELLANEOUS

Lipoic acid (thioctic acid) in its reduced form

$$HSCH_2CH_2CH(SH)CH_2CH_2CH_2CH_2COOH,$$

has sulfhydryl groups which can interact strongly with many toxic metal ions[252] and was suggested as an antidote for mercury poisoning.[253,254] It has also been used in the treatment of Wilson's disease[255] and for arsenic intoxication.[256] This compound also complexes with metal ions via its carboxylic acid group, though such complexes are relatively weak.[257]

The use of synthetic oligopeptides containing three cysteinyl groups, as antagonists for toxic metals has also been reported.[258] The administration of a sufficient quantity of the oligopeptide 15 minutes prior to the administration of cadmium chloride resulted in a significantly higher survival rate than in control animals.

XIII. FUTURE PROSPECTS

There is every reason to believe that certain currently available sulfur compounds will become more important clinically in the treatment of metal intoxications. Dimercaptosuccinic acid appears to be a very promising candidate to replace the widely used, but unpleasant and rather toxic BAL (2,3-dimercapto-1-propanol). The recent discovery that dithiocarbamates can effectively mobilize intracellular deposits of cadmium should lead to an increase in the use of this type of compound, as well as to a broader realization that sulfur compounds often will offer novel routes for the mobilization of other toxic metals from intracellular sites. Most of the commonly used antidotes for toxic metals, such as $Na_2CaEDTA$, $Na_3CaDTPA$ and related compounds are incapable of passing through cellular membranes in amounts large enough to have any significant effect on such intracellular deposits. Because such deposits are often characteristic of the chronic metal intoxication that arises from environmental pollutants (e.g., Cd^{2+}, Hg^{2+}, Pb^{2+}, etc.) an increased comprehension of this problem will lead to a greater interest in membrane-penetrating chelating agents based on sulfur donors for the treatment of such intoxications.

One of the major procedures for the development of new therapeutic chelating agents has been to start with a careful examination of the relevant stability constants.[101] This procedure has worked very well with oxygen- and nitrogen-containing chelates, many of which have had stability constants determined for several dozen metal ions.[102–104] With sulfur-containing chelating agents the situation is quite different. Because of the importance of the side reactions of sulfur compounds (especially oxidation) under the conditions typically used to determine stability constants, very few such sulfur compounds have been extensively characterized in terms of the stability constants of their complexes with toxic metals. Furthermore, for the few that have been studied, there is often a disturbing disagreement about the numerical values which have been reported for a given metal complex. Because of this problem, an alternative approach seems currently more fruitful in the search for new sulfur-containing chelating agents. This starts instead from all of the different kinds of information which are available on the tendency of a chelating agent to bond to a given metal ion (rather than being restricted solely to numerical stability constants)[105] and then develops structure-activity relationships using an appropriate biological model.[106] This approach also has the advantage that it recognizes the great variations which can occur in the biological properties of the metal complexes of a given sulfur donor group as the nature of the carbon skeletons attached to those donor groups is altered.

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