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REVIEW PAPER

Chemistry and Toxicology of Sulphur Mustard—A Review

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ABSTRACT

Bis(2-chloroethyl) sulphide commonly known as sulphur mustard (SM) is highly reactive bifunctional compound, documented as antimitotic, mutagenic, carcinogenic, teratogenic and cytotoxic agent. It is a powerful vesicant and has been employed as a chemical warfare agent. Skin, eyes and respiratory tract are the principal target organs and the deoxyribose nucleic acid (DNA) is the most important molecular target of SM toxicity. There is no specific antidote for SM injury. Treatment to SM toxicity is symptomatic.

1. INTRODUCTION

Bis(2-chloroethyl) sulphide commonly known as sulphur mustard (SM) or mustard gas is a powerful vesicant and has been employed as a chemical warfare (CW) agent of historical and current interest. Mustard gas is also called yperite from the name of the city *Ypres*[1], near which it was used for the first time by Germans in 1917. It was used in the form of an artillery bombardment against British front. SM is a colourless oily liquid, odourless only in its pure form and in ordinary field concentrations, but most of the samples in high concentrations have characteristic odour resembling that of horse radish or oil of mustard, hence the name mustard gas. Compared with properties of an ideal CW agent, mustard gas meets the requirements like high toxicity, extreme multiple effectiveness, high persistency, insidiousness, high boiling point, low volatility, high penetrability, high chemical stability, high specific gravity and vapour density[2-10]

Since World War I, very few studies have been conducted to understand the toxicological effects[11] of SM. After Iran-Iraq conflict, excellent reports on the war victims data and the methods for clinical management have appeared[12-14]

SM is highly reactive bifunctional compound and has been documented as antimitotic, mutagenic, carcinogenic, teratogenic and cytotoxic agent[15]. Since some of its actions are similar to those of ionizing radiation, it is also known as radiomimetic compound. Skin, eyes and respiratory tract are the principal target organs and the deoxyribose nucleic acid (DNA) is the most important molecular target of SM toxicity. SM generally causes severe injury in fur-covered animals because of their thin epidermis and densely-packed hair follicles. The skin from such animals does not vesicate. However, the chemical analysis of lesions caused by SM on experimental animals are similar to the lesions caused in human beings[16]. Due to its very reactive and hazardous

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nature, very few laboratories have taken up research on this compound.

2. PREPARATION OF SM

In the literature, SM is known by synonyms like yperite, mustard gas, SM gas, bi-functional SM, mustard sulphur, schwelfel-lost, s-lost, lost, yellow cross liquid, kampstoffe, 2,2′-dichloro-diethyl sulphide, 1-chloro-2-(2-chloromethyl thio)ethane, beta, beta′-dichloroethyl sulphide, bis(2-chloroethyl) sulphide, and 1,1′-thiobis-(2-chloroethane). This war gas was discovered by Despretz[17] in 1822. It was prepared by the reaction between ethylene and sulphur chloride. After Despretz, SM was prepared by Riche[18] in 1854 and later by Guthrie[19] in 1860, while studying the condensation product of the halogenated sulphur compounds with olefins. Later, SM was prepared by Meyor[20] in 1896 by the chlorination of thiodiglycol with phosphorous trichloride as per the following reaction:

$$S(CH_2CH_2OH)_2 + PCl_3 \rightarrow S(CH_2CH_2Cl)_2$$

Attempts were also made to prepare SM in pure state by Clarke[21], Steinkoff[22] and Ludin[23] by the chlorination of thiodiglycol using *HCl*, thionyl chloride or sulphur mono and dichloride. Pure SM (98 per cent yield) can be prepared using Meyer and Stephen's method[24] by spraying 75 parts of S_2Cl_2 and 25 parts of SCl_2 in an atmosphere of ethylene. The other methods for the preparation of SM of less importance were reported by Dupont chemists[25] in 1945. These were apparently based on earlier work, and involved photochemical addition of H_2S to vinyl chloride. This is brought about by UV irradiation in the presence of peroxide catalysts[26].

$$2CH_2{=}CHCl + H_2S \rightarrow S(CH_2CH_2Cl)_2$$

3. PHYSICOCHEMICAL PROPERTIES

In pure state, SM is colourless, odourless oily liquid, whereas the industrial product is yellow to dark brown and has a characteristic sweetish odour. The melting point of the industrial product is lower than that of pure SM. The physicochemical characteristics[31-37] and spectral data[38-39] of SM are presented in Tables 1 and 2.

The saturation concentration of SM, which amounts to about 0.6 mg/l at 20 °C , suggests a good persistency[27]. Its persistency in the field varies from 36 hr to several days. The persistency dependents on the meteorological conditions, such as temperature and wind velocity. To enhance its persistency and effectiveness, use of various chemicals has been tested over the years. Such chemicals (adjuvants) fall in four main categories: stabilisers, freezing point depressants, carriers and thickeners. Some adjuvants serve more than one of these purposes[28-30].

Impure SM usually containing H_2O or *HCl* has a corroding effect on iron and steel. The iron salts thus formed promote corrosion. Corrosion inhibitors and anti-oxidants (stabilisers) prevent decomposition while in storage. Such agents are tetra-alkyl ammonium halogenides, hexamethylene tetramine, pyridine, picoline, quinoline and other organic amine derivatives. In United States, during World War II, hexamethylene tetramine (1 per cent) was used as a stabiliser for Levinstein mustard, and subsequently, 0.5 to 1 per cent tetramethyl ammonium bromide was also used for this purpose[40-42].

Freezing point depressant for SM is important because pure SM is solid at 14 °C or less and relatively difficult to disseminate efficiently. The ballistic behaviour of a liquid-filled projectile is much altered if its payload solidifies. The solubility of SM in different solvents can be used to lower its freezing point. Such solvents are chlorobenzene, nitrobenzene, benzene, tetra-chloroethane, etc. These can be added in different proportions (up to 25-30 per cent) so as to bring down the freezing point to −1.0 to 3.0 °C, but at the same time these solvents in this proportion will have the diminishing effect of the agent through

Table 1. Physicochemical properties of sulphur mustard

Chemical formula	$C_4H_8Cl_2S$
Chemical name	Bis(2-chloroethyl) sulphide
Common name	Distilled mustard
Molecular weight	159.08
Freezing point (°C)	14.45
Boiling point (°C)	217.5 (with decomposition) 108-109/15 mm 97-98/10 mm
Latent heat of fusion (cal/g)	2.5 at M.P.
Refractive index, n^D	1.531
Vapour density	5.4
Vapour pressure (mm/*Hg*)	
At 0 °C	0.024
at 10 °C	0.054
at 20 °C	0.115
at 30 °C	0.230
Viscosity (poise) at 20 °C	0.459
Specific heat at 25-100 °C (cal/g)	0.330
Latent heat of vaporisation (cal/g)	90.3
Thermal expansion coefficient at 15-80 °C	0.000896
Flash point (°C)	105
Decomposition temperature (°C)	149-177
Incineration temperature (°C)	500
Specific gravity	
at 15 °C	1.2790
at 25 °C	1.2686
at 35 °C	1.2584
at 50 °C	1.2426
at 75 °C	1.2158
Solubility in water	
(g/l)	1.0
(g/l)	0.8
(g/l)	0.6
(mg/l)	4-5
Solubility in organic solvents	Highly soluble except in petroleum ether

dilution. Hence the use of SM-lewisite, SM-phenyl dichloroarsine, SM-diphosgene or chloropicrin is reported in the literature[43].

Table 2. Spectral data of sulphur mustard

Technique used	Spectral data	
IR (neat)	2960 (*C-H* aliphatic) 1440 (*S-C-H*) 700 (*C-Cl*)	
^1H-NMR ($CDCl_3$)	3.650 (2,2′ proton) 2.925 (1,1′ proton)	
$^{13}C(CDCl_3)$	43.07 (2,2′ carbon) 34.64 (1,1′ carbon)	
Mass spectrometry	M/z	Relative densities
	63	262.1
	65	76.8
	95	23.2
	97	5.0
	109	1000.0
	111	341.5
	158	230.4
	160	157.4
	162	33.4

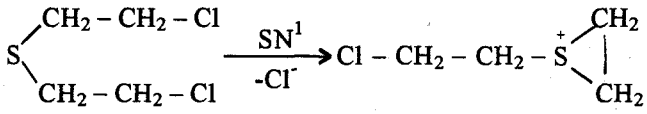
In order to raise the persistency, adhesiveness and consequently the effectiveness of SM, some chemicals are added to it which increase its viscosity. These additives not only guarantee effectiveness for a longer duration, but also hinder/retard decontamination. A good number of polymerisates are suitable as additives, including methyl methacrylate polymerisates with molecular masses from 40,000 to 50,000 and added in proportions of 4-8 per cent. The viscosity of these mixtures is between 30 cp and 600 cp (10 °C). Such mixtures are particularly suitable for spraying from great heights.

4. CHEMICAL PROPERTIES

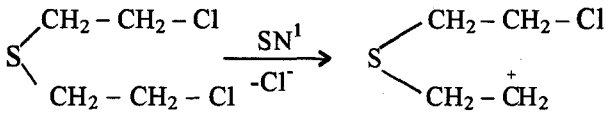
The chemical properties of SM are determined by central sulphur atom (having free electron pairs available) as well as by the side chains. Oxidation is a typical example where the central atom is subjected to electrophilic attack leading to the formation of sulphone and sulphoxides. Another example of electrophilic attack is the formation of sulphonium salts.

4.1 Hydrolysis

The fundamental importance of SM chemistry and toxicology is the formation of heterocyclic onium ions by the interaction between the nucleophilic central atom and the negative inductive effect of the chlorine atoms in the side chains. The kinetics and mechanism of hydrolysis of SM and its monochloro derivatives have been extensively investigated[44-51]. These studies have confirmed that the first step is the formation of transient cyclic sulphonium cation via the intramolecular assistance of the neighbouring sulphur. The cation then reacts quickly with water to form corresponding hydroxyl compounds[52,53].



However, this ion is highly unstable and has never been isolated, making the evidence for this mechanism circumstantial. A second mechanism has been proposed proceeding via a carbocation ion[54].



At higher substrate concentrations in the absence of any organic solvent, however, both dissolution and reaction take place simultaneously[55] and initial product, R-*S*-CH_2CH_2OH from reaction with water accumulates in the aqueous phase and reacts with the ethylene sulphonium cation to form a dimeric sulphonium cation (Scheme I).

4.2 Oxidation

Like all other thioethers, SM tends to add one or two oxygen atoms and gets converted to the corresponding sulphoxide or sulphone by oxidising agents. Some of the oxidation reactions[56-61] are summarised in Scheme II.

N,N-Dichloro-4-methylbenzenesulphonamide (Dichloramine-T) reacts with SM instantaneously, even at sub-zero temperature, to yield *p*-toluene sulphonamide, 2-haloethyl 1-chloro-2-halovinyl sulphide and hydrogen chloride. A homolytic mechanism is proposed for the reaction[62].

4.3 Other Selected Chemical Properties

At ordinary temperature, dichloroethyl sulphoxide is very stable, but on heating it decomposes to hydrochloric acid and toxic gases. This decomposition starts at 150 °C and is complete at 800 °C. Other common reactions of SM are shown in Scheme III.

5. REACTIONS WITH BIOCHEMICALLY-IMPORTANT FUNCTIONAL GROUPS

5.1 Sulphydryl Group

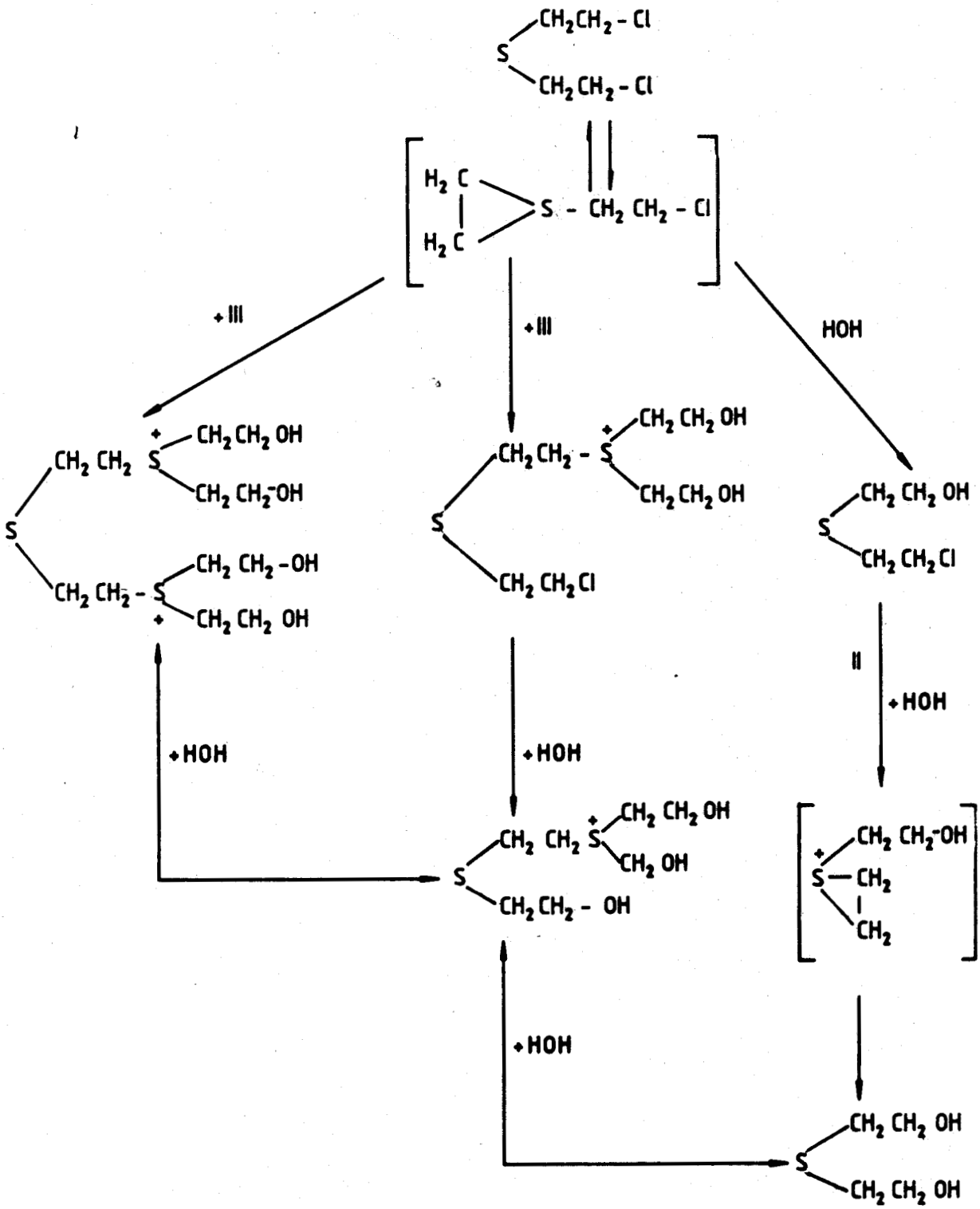
Reactivity of SM with sulphydryl (-*SH*) group is of great biochemical interest as -*SH* containing compounds, e.g., cysteine manifest high competition factors. Under appropriate conditions, one molecule of SM can alkylate and thus crosslink two molecules of -*SH* containing compounds, e.g., bis-*S*-cysteinyl derivative of SM. The products of reaction of SM with -*SH* containing compounds are highly stable at physiological p*H* and temperature.

5.2 Carboxyl Group

Both SM and hemi-sulphur mustard alkylate carboxyl groups to form saponifiable esters of thiodiglycol [63]. This reaction is also of biochemical significance as carboxyl group is present in amino acids and metabolites of intermediary energy metabolism.

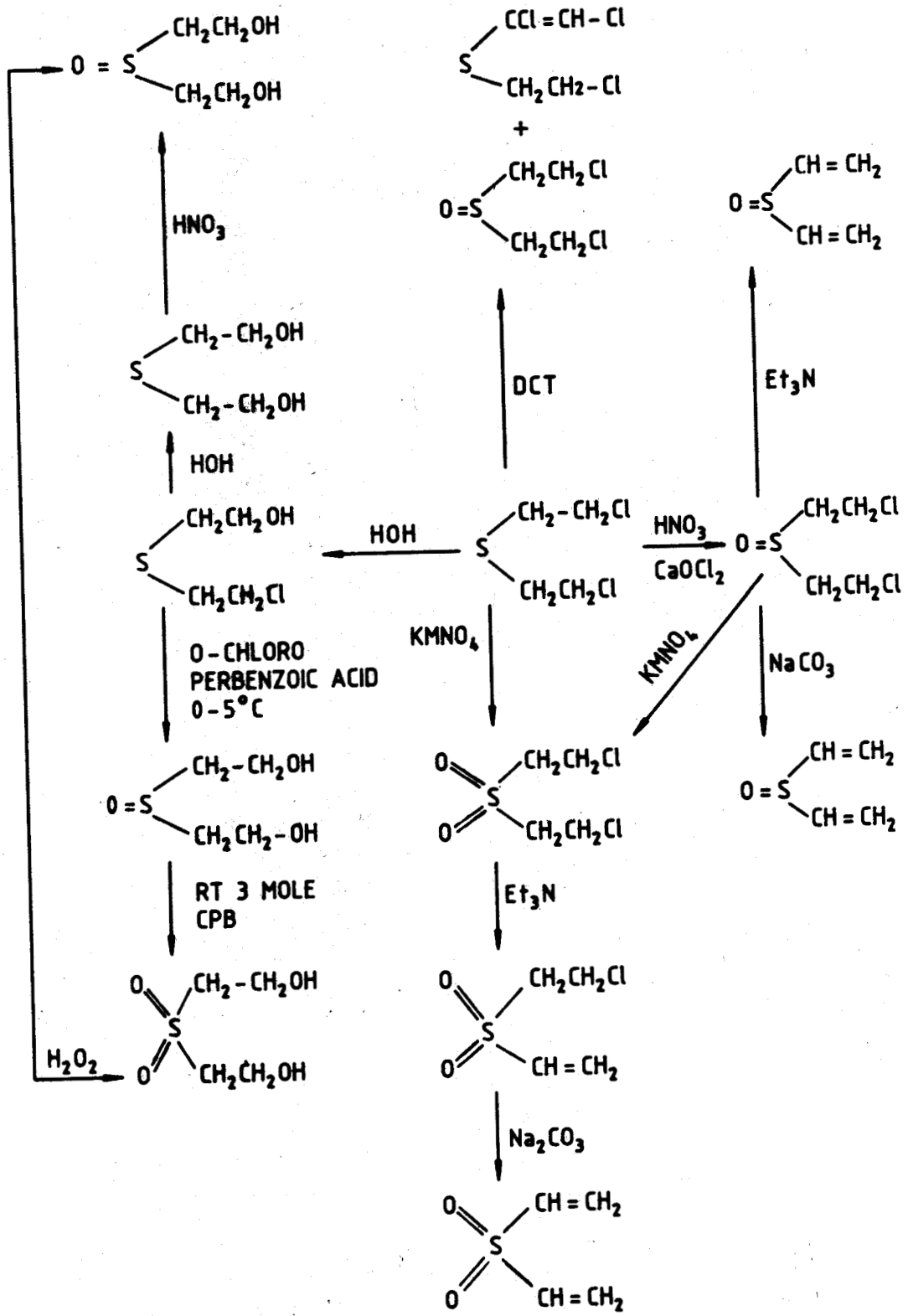
5.3 Organic & Inorganic Phosphates

The research activities carried out to study reactions of SM with phosphates do not commensurate with their significant biological role. The dithiophosphate ion has the highest competition factor not only among inorganic phosphates but with all compounds studied till date.

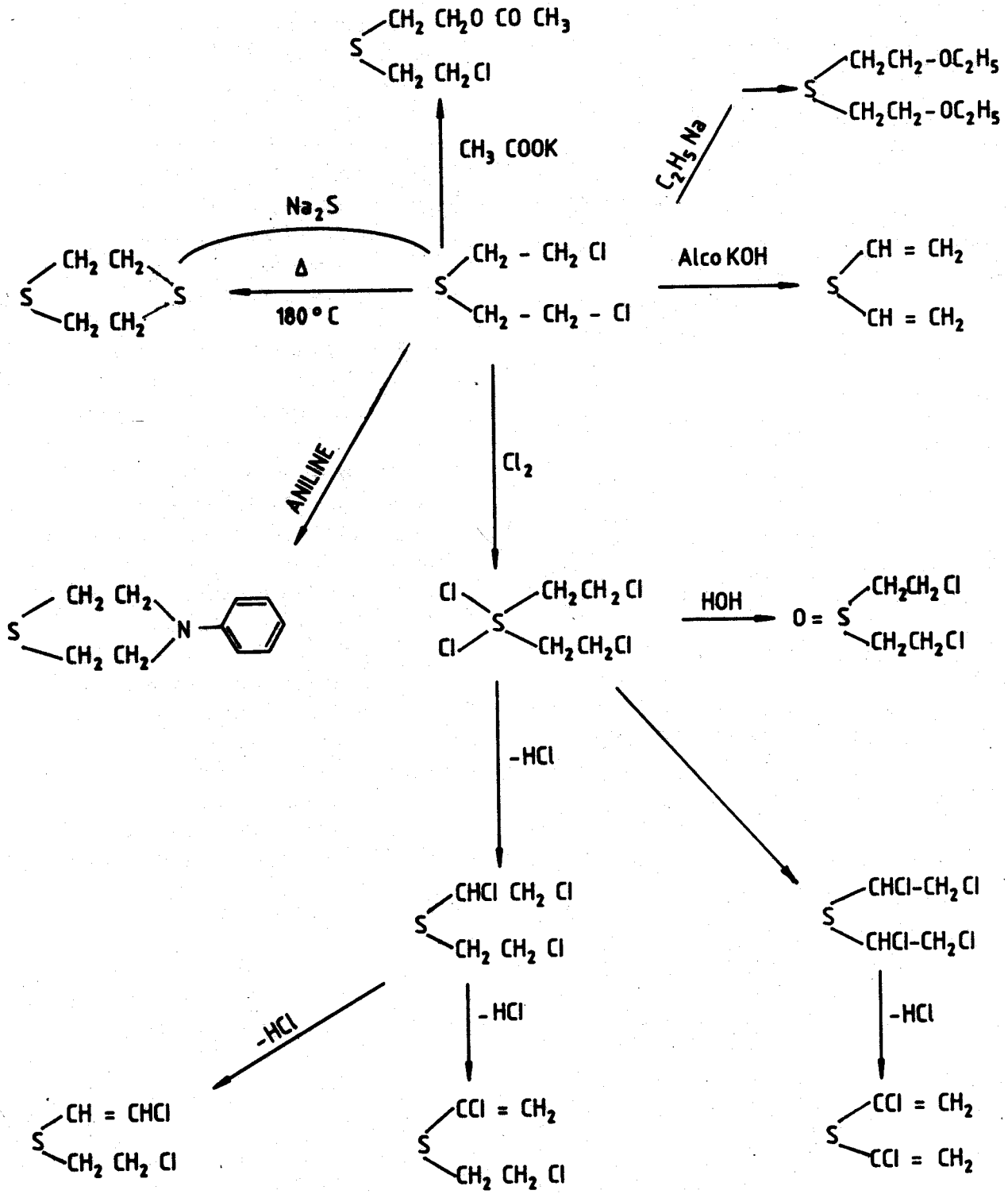


Scheme 1. Mechanism of hydrolysis of SM

Data is not available for biochemically-important phosphorous containing compounds, viz., energy carrying substrates, nucleic acid precursors, nucleoside, deoxynucleocide di- and triphosphates and products of phosphoinositol metabolism. However, it is not known if electron donating



Scheme II. Oxidation reaction of SM



Scheme III. Some selected reactions of SM

Table 3. Toxicity data of SM

Threshold level in man (mg/m^3/min)	
Eye	5
Skin	150
Inhalation	50
Incapacitation level in man (mg/m^3/min)	
Eye	200
Skin	1,000
Inhalation	300
Median lethal level in man (mg/m^3/min)	
L_{ct50}	
Skin	1,500
Inhalation	10,000
LD_{50} *(in animals)* (mg/kg)	
Mouse (percutaneous)	154.71
Rat (male, percutaneous)	169.11
Rat (female, percutaneous)	180.70
Rabbit (percutaneous)	120.00
Guinea pig (percutaneous)	100.00
Cat (percutaneous)	89.00
Dog (percutaneous)	126.00
Rabbit (oral)	20.00
Guinea pig (intraveneous)	9.00

ability of phosphate is influenced by neighbouring phosphate groups in a polyelectrolyte like sugar-phosphate backbone of nucleic acids [64].

5.4 Reactions with DNA

Bifunctional SM gives three major products of alkylation identified till date, of which two are monofunctional adducts and one crosslinked adduct involving guanines on the same strand or complementary strands of DNA. The alkylated purines, 7-alkyl-G and 3-alkyl-A are unstable and are released spontaneously from SM-treated DNA at physiological p*H* and temperature by cleavage of the N^9-glycosidic bond giving rise to apurinic sites[65]. This has been related to the formation of DNA breaks leading to cytotoxicity of SM. Doskocil[66], *et al.* have studied the reaction kinetics of DNA with SM in detail.

5.5 Reactions with RNA

The interaction of SM with RNA and ribonucleoproteins has not been investigated extensively. Shooter[67], *et al.* studied the reaction of bacteriophage RNA with SM. They have identified 7-alkyl-G as principal alkylation product with both SM and hemi-sulphur mustard by comparison of chromatographic profiles, physicochemical characteristics and spectral properties of the acid hydrolysate of alkylated RNA with those of synthetic marker substances of known structures. In some experiments, the products were compared with those obtained by acid hydrolysis of the alkylated homoribonucleotides poly A, poly G and poly C. Reaction with hemi-sulphur mustard also produced 1-alkyl adenine, 3-alkyl adenine and 3-alkyl cytidylic acid to a much smaller extent.

Malbon and Parish[68] reported that the RNA alkylated by SM was highly stable and remained essentially undegraded even on 25 per cent of all guanine the alkylation. Abell[69], *et al.* have reported the alkylation of terminal phosphomonoester in poly (U) by SM leading to inactivation of template for polypeptide synthesis. Venilt[70], *et al.* reported that transcription in bacteria for β-galactosidase is about five times more sensitive to translation. Bifunctional SM-produced crosslinks in RNA, however, did not affect the function of translation and hence, it can be presumed that crosslinking in RNA has less biological consequences.

5.6 Reactions with Proteins

Cyclic ethylene sulphonium cation is highly electrophilic with great affinity for negatively charged or uncharged functional groups. At p*H* 6 to 8, carboxyl, imidazole, thiomethyl and sulphydryl groups of proteins would be negatively charged and expected to react, to a significant extent with SM. Heriott[71], *et al.* reported that SM could preferentially react with carboxyl groups in proteins at p*H* 6 as the number of carboxyl groups esterified by SM was equal to the total number of SM residues bound to the protein. Davis and Ross[72]

observed that at p*H* 7.5 the carboxyl groups of oxyhaemoglobin and serum albumin were extensively esterified by SM.

Banks[73], *et al.* used radioactive labelled (^{35}S) SM in their experiments with ovalbumin and keratin. The ratio of SM adducts to reduce -*SH* groups due to alkylation of these proteins was 10:1. Thus, it was concluded that -*SH* groups in proteins are considerably less reactive than in free amino acids, e.g., cysteine or glutathione. SM sulphone was reported to be more reactive with -*SH* groups.

Boursnell[74], *et al.* have studied the reaction of SM and its sulphone derivative with proteins. They reported that antibodies against SM-treated proteins and sulphone-treated proteins did not cross react. SM sulphone-treated proteins were antigenically different to SM-modified proteins because of the high reactivity of sulphone with amino groups of protein.

SM adducts from proteins could not be easily removed under physiological conditions. Alkaline hydrolysis cured the proteins of SM adducts but the cells cannot tolerate such conditions. Pierie[75] noted that SM-treated collagen from Ox cornea could partially regain its native properties on alkaline hydrolysis.

6. RELATION BETWEEN CHEMICAL STRUCTURES & PHYSIOLOGICAL EFFECTS

The presence of halogen atoms in the SM molecule is a prerequisite for the skin damaging effect, that too on the 2,2′ carbon atom of the molecule. The disubstitution products in the 1,1′ position are less effective or not effective at all. Although bis(2-bromomethyl) thioether and bis(2-iodoethyl) thioether show the same physiological behaviour as bis(2-chloroethyl) thioether, they are weaker in toxicity than this compound, but it must be assumed that its effects are same.

Introduction of additional halogen atoms which leads to asymmetry of the halogen thioether molecule diminishes its toxicity. These compounds have little or no blistering effect, e.g., 1,2,2′ -trichlorodiethyl thioether. The physiological effectiveness is reduced by the presence of two or more mutually bonded thiosulphur atoms in the molecule. Introduction of one or more methylene groups up to a maximum of $n = 5$ between two sulphur atoms leads to a powerful skin damaging effect which declines at $n > 5$. The oxidation products of SM, such as sulphoxide and sulphone have little toxicity and skin damaging effects.

7. EXTRACTION & ANALYSIS

Various methods have been employed for the extraction and analysis of SM[76-85]from time-to-time. These methods include: thin layer chromatography (TLC) identification, gas layer chromatography (GLC) retention indices, gas chromatography-mass spectrometry (GC-MS) and high performance liquid chromatography (HPLC) methods. Comparative account of various methods for qualitative and quantitative identification of SM and its metabolites from the body fluids and tissues is described by Somani[86], *et al.*

8. TOXICODYNAMICS OF SM

8.1 Routes of Entry

Any foreign compound may enter the body through ingestion of food and drink, inhalation, or by absorption through skin. They, in turn, undergo biotransformation by the action of different metabolising enzymes. Enzyme systems capable of carrying out oxidation, reduction, hydrolysis, etc, (phase I reaction) and conjugation of some of the metabolic products with endogenous compounds like glycine, glucuronic acid, etc. (phase II reaction) are present in liver and other organs[87]. Skin, eyes and respiratory tract are the major exposure routes which have primary military

relevance for entry of vesicants. SM is highly lipophilic and can rapidly penetrate all epithelial tissues. The toxicity data of SM[88] is given in Table 3. Epithelial concentrations of SM could be large enough, although transient, to cause local cytotoxicity and necrosis at sites of absorbtion. It is easily absorbed by the body fluids and quite rapidly spreads throughout the body.

Axelrod and Hamilton[89], while working with radioactive SM and lewisite, observed that SM was easily absorbed through hair follicles. Sinclair[90] also observed that SM could penetrate the moist skin more easily than dry skin. Even at lower doses, SM may cause blistering at the back of the hand. Due to the presence of *stratum corneum,* the layer of dead epithelial cells in palms and soles, the blistering in palms and soles is prevented. Since *stratum corneum* is absent in eyes and respiratory tract contrary to skin, the eyes and respiratory tract epithelium presents no barrier to SM absorption.

8.2 Absorption & Distribution

As reported by Renshaw[91], 80 per cent of liquid SM applied to skin evaporates and only 20 per cent penetrates it. At 21 °C, liquid SM or saturated vapours penetrate human skin at the rate of 1-4 $\mu g/cm^2/min$. The rate of penetration increases with increase in temperature. About 12 per cent of absorbed SM is estimated to be *fixed* in skin and the remaining 88 per cent is systemically absorbed as *free* SM. Sinclair[92] failed to find any evidence for the active or facilitated transport of SM at cellular level.

The rate of absorption of SM varies from species to species. In rabbits, the rate of absorption is different from human beings. Cullumbine[93] observed free SM in the rabbit skin a day after cutaneous exposure. In contrast, Drasch[94], *et al.* observed milligram levels of free SM in several organs in human beings even after seven days of exposure. Hambrook[95], *et al.* reported that 75 per cent of (^{35}S)-SM vapour could pass through the skin and was systemically distributed in rats. They also observed that SM could be absorbed by blood and retained in red blood cells up to 65 days.

Local distribution of (^{35}S)-SM at sites of absorption in human skin showed a major portion of radioactivity in epidermis and slightly less in dermis, 24 hr after exposure. In rabbit eyes, SM was observed primarily in the cornea within five minutes after exposed to vapours with lesser amounts in the iris, lens and conjunctiva. Radioactive SM was administered either intravenously or percutaneously in mice by Clemedson[96], *et al.* They observed increased levels of radioactivity in tissues after five minutes of intravenous injection and 15 min after percutaneous application. Almost all radioactivity seen after intravenous injection was eliminated within four hours. Following dermal exposure, a significant amount of radioactivity remained in the body for hours and could be located in intestine even after few days. After percutaneous application, much of the radioactivity remained in the skin, at or near the site of application, even after four days. Slow and continuous uptake of radioactivity following cutaneous application was the reason suggested for slow clearance of radioactivity.

A similar study with radioactive SM was carried out by Boursnell[97, 98], *et al.* in rabbits where distribution of radioactivity after intravenous injection was in the order of kidney > lung > liver. The levels of radioactivity in kidney and liver were highest at one hour whereas for lungs, it was the highest at four hours. About 10 per cent of injected radioactivity was found in the bile and duodenal walls. Maisonneuve[99], *et al.* found rapid distribution of radioactivity in several tissues (within minutes) following intravenous injection of [^{14}C] -SM (10 mg/kg) in rats. A significant amount of ^{14}C activity was detected in kidney, liver, lung, intestine and stomach. All these organs are associated with elimination and transformation process.

8.3 Biotransformation of SM

Radio-labelled SM was administered through intravenous injection[100,101] and intraperitoneal injection[102] and the urinary products were isolated and identified. Both reported around 15-20 per cent radioactivity in urine related to one compound. Glutathione-bis-chloroethyl sulphide conjugates, and cysteine-bis (B-chloroethyl) sulphone as major product was observed in urine, suggesting that through intravenous injection, SM comes in direct contact with glutathione present in abundance in the blood and reacts directly with it to form cysteine-bis(B-chloroethyl) sulphone.

Wils[103,104], *et al.* found that significant amount of thiodiglycol was present in human urine more than a week after presumed SM exposure in Iran-Iraq casualties. Based or *in vitro* data, Yang[105], *et al.* suggested that SM might have formed sulphonium salts *in vivo* which accounted for relatively longer lasting SM or thiodiglycol in human urine.

Recent international events emphasised the need for procedures to provide forensic evidence and to confirm diagnosis of poisoning by SM. The studies on the fate of SM in animals is necessary to acquire relevant knowledge and to develop procedures based on the analysis of biological samples. Presently, limited information on the fate of SM in animals, its distribution in tissues, persistence and metabolism is available.

Hambrook[106], *et al.* studied the biological fate of SM in urinary and faecal excretion of rats after injection or cutaneous application of radio-labelled SM (^{35}S)-SM which indicated that more than 70 per cent of the applied dose was excreted through urine.

Investigations were conducted at the Defence Research & Development Establishment (DRDE), Gwalior, to understand the renal clearance of SM in experimental animals (rat and guinea pig) for preliminary studies and then extended to mice tissues homogenate for identification of SM and its metabolites using HPLC[107] and mass spectrometry[108].

9. EFFECTS OF SM POISONING

The effects of mustard gas on skin range from itching and painful inflammation (resembling a first degree burn) to the formation of large liquid-filled blisters. In the latter case, there is a considerable risk of secondary infection. SM attacks moist areas of the body, such as the neck, armpits, the genitals and chest, or under the breasts most severely. It also irritates the eyes and the eyelids may become swollen. Direct contact of eyes with liquid SM may induce injuries to the cornea and the iris, leading to permanent blindness. After inhalation, SM causes lung oedema but severe intoxications may be fatal. The symptoms are reminiscent of injuries to bone marrow, lymph nodes and spleen and the resulting drop in white blood cells makes the victim very susceptible to infections. Recently, the effect of SM on laboratory animals has been studied to get an insight into the mechanism of toxicity and also to develop a suitable antidote[109]. The study also envisage the significant protection offered by flavonoids, vitamin E and repeated dose of glucose-saline. Balali-mood[110], *et al.* reported that diagnosis of SM poisoning could be made at an early stage, based on clinical and toxicological findings. The common complications and delayed toxic effects in 1428 SM victims were found in the respiratory tract (90 per cent), skin (88 per cent), eyes (78 per cent), nervous system (71 per cent), gastrointestinal tract (55 per cent) and sexual lungfibrosis (62 per cent) were the main respiratory disorders observed.

9.1 Immunotoxic Effects

Alkylating agents are reported as immunotoxic. The immunotoxic potential of monofunctional SM, butyl-2-chloroethyl sulphide and nitrogen mustard has been studied at large. Neeraja[111] has reported the immunotoxic effects of SM in experimental animal model and also screened different

radioprotectors and anti-inflammatory drugs against its systemic and dermal toxicity. They observed that WR-2721, [S-2(3-aminopropyl amino)] ethyl phosphoro thioic acid and thiol containing compounds *N*-acetyl cystine (NAC) and dimercapto succinic acid (DMSA) offered better protection in SM-treated animals.

9.2 Mutagenic Effects

Several studies have documented the mutagenic effects of SM in mammalian cells, in a wide variety of animal species and also in *in vitro* test systems. The genetic toxicity of SM has been reviewed by Fox and Scott[112]. Further, the mutagenic potential of SM was evaluated in the standard plate incorporation version and the pre-incubation modification of the *Salmonella/* microsomal assay. Significant enhancement in the frequency of sister chromatid exchanges has been reported in the peripheral lymphocytes obtained from the fishermen who were exposed to SM in the Balti sea[113,114].

9.3 Effects on Gastrointestinal Tract

Ingestion of SM-contaminated food and water can produce deleterious effects on gastrointestinal tract resulting in nausea, vomiting and diarrhoea. Gastrointestinal tract mucosal necrosis, membrane damage, severe abdominal pain, bloody diarrhoea and possible collapse resulting in loss of electrolytes, and dehydration may also occur. In general, SM exposure results in dizziness, anorexia, lethargy and general malaise.

9.4 Reproductive & Developmental Effects

Relatively little is known concerning the effects of SM on development and reproduction. Chronic exposure to SM and the reproduction abnormalities were observed by several workers, including foetal malformation and foetal mortality [115]. Further, there is also evidence that analysis of sperm, morphology data obtained from SM-treated male rats showed a significant decrease of sperm count and increase of abnormal sperm counts. Azizi[116] also observed a significant low sperm count in SM victims.

10. ANTIDOTES & METHODS OF TREATMENT

Several prophylactic and therapeutic approaches have been tried by workers with more than hundred compounds. There is no specific antidote for SM injury. Treatment to SM toxicity is symptomatic. By far, the most important measure is to rapidly and thoroughly decontaminate the victim and thereby prevent further exposure. Clothes should be removed and skin be decontaminated with a suitable decontaminant, and washed with soap and water. If hair is suspected to be contaminated, it must be shaved off. Eyes should be rinsed with water followed by rinsing with physiological salt solution for at least five minutes. Several compounds like calcium hypochlorite (bleaching powder), potassium permanganate, Fuller's earth, chloramine-T and *N*, *N'*-dichloro-bis(2,4,6-trichlorophenyl) urea have been used as decontaminants against SM. A combination of *N*, *N'*-dichloro-bis(2,4,6-trichloro-phenyl) urea (CC-2) and Fuller's earth (BPC standard) was reported as an efficient decontaminant mixture[117].

The symptoms of systematic poisoning are similar to those of radiation exposure. Hence, efficacy of different radioprotectors and sulphur containing compound that prolong the survival, were evaluated by Neeraja[111]. Balali-mood[110], *et al,* reported that NAC was found to give good protection by preventing the toxicity caused by SM.

The conventional treatment of human beings for poisoning by SM includes physicochemical procedures and medical measures. However, excluding decontamination as a standard first aid treatment, medical measures, as it is known, are more empirical than rationally established. Several investigators have screened a number of antidotes for protection against SM toxicity[118,119]. Wormser[120] showed that a nontoxic and nonirritant iodine/povidone iodine agent, a percutaneous

preparation efficiently protects guinea pig skin from SM poisoning even when applied 20 min after exposure.

As SM-induced skin pathology resembles that of thermal burns, investigations were carried out to understand the protective action of saline or glucose saline along with the blood acid-base status and electrolytes. The results revealed that the utility of saline and glucose-saline treatment in providing protection against SM poisoning in mice, probably was through the replenishment of fluid loss and the electrolyte loss locally[109].

Sodium thiosulphate is a well-documented antidote for SM poisoning[121-123], but it is effective only in very high doses and has to be administered before exposure to SM as it reacts only with cyclised form. However, subsequent investigations have shown that it can be administered effectively after SM intoxication. It was also found that sodium thiosulphate gave protection by increasing the survival time and preventing the fall in the body weight induced by SM.

Recently, Sugendran,[124] *et al.* have tabulated the drugs and chemicals tested for their antidote efficacy against the toxic effects of SM on war victims and also on laboratory animals.

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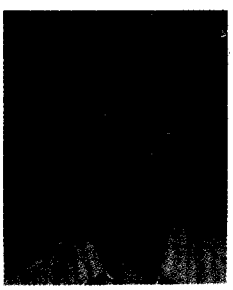

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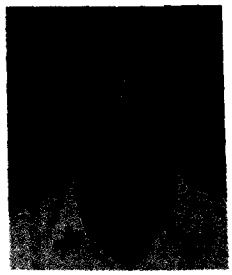

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