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Progress in the Search for Chemical Protective Agents against Radiation

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Information published during 1968–1973 on the search for protective agents, capable of preventing or diminishing the harmful action of ionising radiation, is discussed and analysed. Only synthetic monomers belonging to various classes of organic compounds are considered: the search for protective compositions is not discussed. The bibliography comprises 168 items.

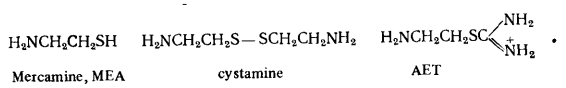
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I. INTRODUCTION

A quarter of a century has elapsed since the first demonstration that chemical protection of animals from ionising radiation was possible[1,2]. During this period an immense amount of work has been done on synthesising and studying the prophylactic radiation-protective action of several thousands of synthetic and natural substances of diverse structure. Among them have been discovered extremely effective protective agents, capable under experimental conditions of preventing the death of a considerable proportion of animals subjected to X-rays and γ-rays. It can be concluded from the results that the living organism can in principle be protected by means of chemotherapeutic agents from ionising radiation, but considerable difficulties arise in applying such protection to man, since there is no proof that the doses of these agents that he can tolerate are able to protect him from the action of radiation. The whole 25-years' period of development can be arbitrarily divided into three stages.

The initial stage, from 1949 to the mid-1950s, saw the discovery of protection by chemicals and the start of the search for such agents among various classes of chemical compounds. The second stage, from the mid-1950s to 1968, extended the search for substances which would diminish radiation damage in animals, with a deeper study of compounds showing the greatest protective effect in experiments and attempts to bring the most effective of them to clinical application. An achievement of this stage was the production of such protective preparations as 2-aminoethanethiol (mercamine, MEA), the corresponding disulphide (cystamine), and *S*-2-aminoethylthiouronium bromide hydrobromide (AET)



Mercamine, MEA cystamine AET

However, the considerable toxicity and the narrow therapeutic spectrum of these products made it urgently necessary to find more efficient protective agents. By the end of the 1960s, after many different chemical compounds had been studied (~ 3000 by 1965), the impression was created that chemical protection from radiation was of only theoretical importance, and preparations better than the above three could not be obtained. It was even suggested that the whole idea of protection from ionising radiation by means of chemical substances was unpromising.

In this connection one of the pioneers of chemical protection (Bacq) wrote: "... a tendency has become evident to overlook the possibility that new protective chemicals might appear and to focus attention on studying the most active of known agents. However, it is not impossible that more active and far less toxic chemical protective agents will be discovered in the near future".[3] These words of Bacq's have proved to be prophetic: indeed, publication started to appear in 1968 which marked the beginning of the current stage in the development of chemical protection of the living organism from ionising radiation. This stage has seen considerable advances in the production of protective agents and, most importantly, the establishment of confidence in the reality of the practical application of chemical prophylactic radiation-protective agents. The number of substances that have been synthesised and studied as potential protectors has been rapidly increased by slight variations on the optimum chemical structures discovered previously. The main aim has been to find agents of great therapeutic spectrum; the results up to 1971 have been covered in brief reviews[4,5].

The present Review studies and analyses results, published from 1968 to 1973 inclusive, of the search for monomeric synthetic prophylactic protective agents. The greatest attention has been paid during this period, as in previous years, to the search among compounds based on the 2-aminoethanethiol structure. Interesting results have been obtained also for other sulphur-containing compounds and heterocycles.

Before the main subject of the Review is discussed, brief consideration must be given to the quantitative assessment of the efficiency of radiation-protective agents, a problem which has been faced repeatedly[3,6]. American authors[7] have suggested a "protective index"

$$I = \frac{LD_{50}}{ED}\left(1 + \frac{a}{100}\right),$$

representing both the degree of protection and the therapeutic spectrum for a given substance, where LD_{50} is the dose of the agent causing the death of 50% of the animals and a is the percentage survival of the animals with the given effective dose ED and complete mortality in a control group. This parameter has limited application,

since it permits comparison of the efficiencies of substances only under identical experimental conditions (mode of introduction, time of administering substance before irradiation, species of animal, dose and dosage rate of radiation, etc.). However, since the experimental conditions have been adequately standardised during recent years, the protective index can in many cases be used to estimate the practical prospects. Table 1 gives a scale of efficiencies of protective agents based on the protective index and adopted by several American authors.

Table 1. Scale of efficiency of protective agents.

I	0—1	2—5	6—10	11—44	⩾ 15
	0* ineffective	+ relatively ineffective	++ moderately efficient	+++ efficient	++++ highly efficient

* It is assumed that $I = 0$ when protection is below 20%.

The protective index will be used where possible in the present Review. Since the vast majority of experiments with protective agents have been made on mice with the substances introduced 15–30 min before irradiation at 40–400 rad min^{-1}, and the survival rate of the animals was determined after 30 days, these conditions may not be satisfied in the text of the Review.

II. SULPHUR-CONTAINING COMPOUNDS OF AMINOTHIOL STRUCTURE

Among the sulphur-containing compounds studied during the past five years as prophylactic protective agents the vast majority are *N*-substituted derivatives and analogues of 2-aminoethanethiol-thiols, disulphides, thiosulphates, thiophosphates, thiazolidines, etc.—as well as similar compounds in which the ethylene chain has been modified. A considerably smaller number of other sulphur-containing compounds have been studied. They will be discussed in this sequence.

1. *N*-Substituted 2-Aminoethanethiols

Although 2-aminoethanethiol itself has a fairly high protective effect under experimental conditions, its practical use is prevented by its narrow therapeutic latitude of action. With intraperitoneal (ip) injection LD_{50} = 250 mg kg^{-1}, and in the optimum dose ED = 150 mg kg^{-1} it protects 87% of mice when a control batch shows complete destruction; with oral (or) introduction LD_{50} = 615 mg kg^{-1}, ED = 300 mg kg^{-1}, and a = 73%: hence for mercamine

$$I_{ip} = \left(1 + \frac{87}{100}\right)\frac{250}{150} = 3.1,$$

$$I_{or} = \left(1 + \frac{73}{100}\right)\frac{615}{300} = 3.6.$$

On the above scale [Table 1] mercamine must be regarded as a relatively ineffective protective agent. Naturally, therefore, numerous attempts have been made in recent years to vary the structure of mercamine in every possible way in order to obtain a product with the same level of protection against radiation but with a greater latitude of action, i.e. one which is less toxic and better tolerated.

Earlier investigations on the effect of the anion on the protective activity of mercamine have been continued by a detailed examination of its adenosine triphosphate salt [9]. This agent, termed Tsitrifos, was closely similar to aminoethanethiol hydrochloride in activity, but exhibited a protective effect on prolonged irradiation at 10.7 and 3.75 rad min^{-1}.

Various workers have prepared and studied many derivatives of the type

$$RHNCH_2CH_2SH$$

(I)

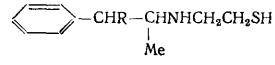
with different *N*-substituents, but most of them were relatively inactive or possessed a weak protective action. Replacing an amino-hydrogen atom by a straight- or branched-chain alkyl results in disappearance of the protective activity [10]. Compounds having a long normal alkyl chain (I: R = C_8H_{17}, C_9H_{19}, $C_{10}H_{21}$) exhibit a protective effect [11]. Polymethylene-*NN'*-bis-2-aminoethanethiol derivatives (II) containing n = 6–8 CH_2, [12] as well as their sulphone analogue (III), [13]

$$HSCH_2CH_2NH{-}A{-}HNCH_2CH_2SH$$

(II) A = $(CH_2)_n$ (III) A = SO_2

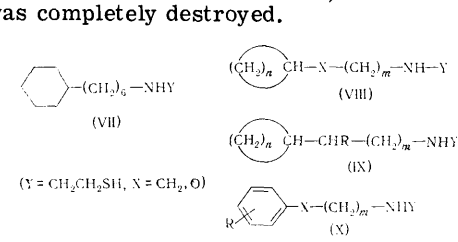
increase very slightly the radiation resistance of mice on prophylactic application. Quaternisation of the nitrogen atom produced a sharp increase in toxicity and a loss of activity, as has been observed with thiocholine (IV). [14]

$Me_3\overset{+}{N}CH_2CH_2SH$ (IV)



(V, R=H); (VI, R=OH)

Little or no protective effect is shown by aminoethanethiol derivatives containing alicyclic, aryl, and heterocyclic substituents attached to the nitrogen atom either directly or through 1–4 methylene groups [10,15]. Similar results were obtained in a study of *N*-substituted derivatives containing hydroxy-, alkoxy-, and aryloxy-alkyl substituents, and of aminoethanethiols with structures (V) and (VI) based on amphetamine and ephedrine [10]. Only one of the 58 such compounds examined in this work, 2-*N*-6'-cyclohexylhexylaminoethanethiol (VII), showed high protection against radiation: an intraperitoneal dose of 30 mg kg^{-1} given 15 min before irradiation provided almost complete protection for mice, whereas a control group was completely destroyed.



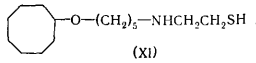
(VII) (Y = CH_2CH_2SH, X = CH_2, O)

(VIII) (IX) (X)

It was probably on the basis of these results that a group of investigators headed by Westland studied in 1972 [16] a series of compounds of type (VII) in which the substituent was an alicyclic ring (VIII) and (IX) or a benzene ring (X) attached by a polymethylene chain (C_3–C_6) either directly or through an oxygen atom to the amino-group, in some of which the polymethylene chain was branched (IX). Cycloalkylalkyl derivatives (VIII) were

considerably more toxic than aminoethanethiol itself and its closest analogues. Most of them, however, had a protective action in smaller doses (25–50 mg kg^{-1}, only 33–17% of the effective dose of 2-aminoethanethiol). Replacing a five-membered by a six-membered ring and varying the length of the polymethylene chain from three to six units had no significant effect on the protective activity of such compounds. Branching in the hydrocarbon chain leads to loss of or diminution in activity. The protective index of the most active does not exceed 3.5, which corresponds to the efficiency of aminoethanethiol itself.

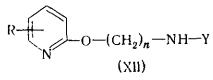
The sole exception among compounds of this type was the cyclo-octyloxypentyl derivative



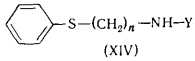
(XI)

While possessing considerably lower toxicity (LD_{50} = 180 mg kg^{-1}) than the other cycloalkylpolymethylene analogues, a 50 mg kg^{-1} dose of this compound protected 83% of mice when destruction in the control group was 100%, and its protective index I = 6.6.

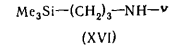
Aryloxyalkyl derivatives (X: X = O) were on the average rather more effective than their alicyclic analogues[16,17]. Among them compounds having n = 4–6 were the most active: the ethylene and trimethylene derivatives did not protect animals[13]. Increasing the number of alkyl substituents in the benzene ring diminishes the protective activity.



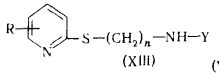
(XII)



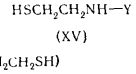
(XIV)



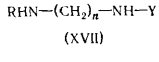
(XVI)



(XIII)



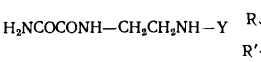
(XV)



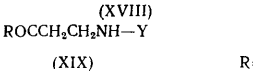
(XVII)

(Y = CH_2CH_2SH)

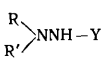
Among the 25 pyridyloxyalkyl derivatives of aminoethanethiol of type (XII) Westland and his coworkers[8] were unable to discover one which would have merited attention as a protective agent. Nor did the pyrid-2′-ylthioalkyl (XIII) and phenylthioalkyl (XIV) analogues, the N-mercaptoethyl (XV)[18] and N-trimethylsilylpropyl (XVI)[19] derivatives, possess a protective action.



(XVIII)



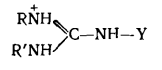
(XIX)



(XX)

R = R′ = Me; R = H, R′ = C_8H_{17}

R = H, R′ = $PhCH_2CH$(Me)



(XXI)

R = R′ = H, Me

Y = CH_2CH_2SH

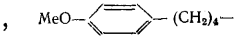
A few compounds have been studied whose alkyl substituent contains a secondary amino-group (XVII), but no active substance was discovered among them[20,21]. The oxamido-derivative (XVIII) had a slight protective effect[22]; replacing a hydrogen atom in the terminal carbamoyl group by phenyl, cyclohexyl, or pyridyl led to a loss of activity. A protective action was evident with derivatives containing a propionic acid residue attached to the amino-group (XIX)[21]; the most active was the amide (R = NH_2), which was followed by the acid (R = OH), the nitrile, and the ethyl ester (R = OC_2H_5). Replacing the amino-group in 2-aminoethanethiol by hydrazino (XX) leads to a loss of protective activity[10]. N'-Methylated derivatives (XXI) showed a considerably weaker protective action than did guanidinoethanethiol[24].

Thus in only one case, N-cyclo-octyloxypentylaminoethanethiol (XI) (I = 6.6), did the wide variation in the structure of the substituent attached to the nitrogen atom in 2-aminoethanethiol (~ 130 such compounds were studied) yield a considerably more effective protective agent.

(XXII, R=H) $(RNHCH_2CH_2S)_2$

(XXIII, R=  –A

a A=CH(Me)$(CH_2)_3$–; b A=$CHCH_2$(Et),



(XXIV)

Aminoalkyl disulphides have aroused considerably less interest in investigators during recent years. The first member of this group, cystamine (XXII), while having several advantages over the corresponding amino-thiol (mercamine), must also be regarded as a relatively ineffective radiation-protective agent (with LD_{50} = 320 mg kg^{-1}, in the optimum dose (intraperitoneal) of 220 mg kg^{-1} it protects ~ 70% of mice[3]: i.e. I = 2.5). During the past 5–6 years great attention has been paid to the preparation and study of derivatives of (XXII) containing N-alkyl substituents substituted by cycloalkyl and cycloalkoxyl, aryl and aryloxyl, pyrid-2-yloxyl and quinol-2-yloxyl. Active compounds have been found among the cycloalkyl and aryl derivatives[13,16,17]; their heterocyclic analogues possessed no protective action[8]. The highest protective efficiency was found with bis-2-N-4′-cyclohexylpentylaminoethyl (XXIIIa)[16] and bis-2-N-4′-p-methoxyphenylbutylaminoethyl (XXIV)[17] disulphides, with the respective protective indices 8.4 and 11.0. It is interesting that the disulphide (XXIIIb), a close analogue of (XXIIIa) whose N-substituent differs by only one methylene unit, has no protective effect[16].

Table 2. Protective properties of amino-thiols and disulphides.

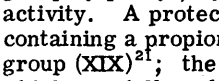
R	$RHNCH_2CH_2SH$				$(RHNCH_2CH_2S-)_2$				Ref.
	dose, mg kg^{-1}		protection, %	I	dose, mg kg^{-1}		protection, %	I	
	LD_{50}	ED			LD_{50}	ED			
cyclo-$C_6H_{11}CHMe(CH_2)_3$–	75	50	17	0	45	10	85	8.4	16
cyclo-$C_6H_{15}O(CH_2)_5$–	180	50	83	6.6	560	160	50	5.8	16
2,6-$Me_2C_6H_3O(CH_2)_4$–	75	50	80	2.7	560	160	17	0	16
2,3,6-$Me_3C_6H_2O(CH_2)_4$–	130	100	33	1.7	56	32	50	2.2	16
4-$MeOC_6H_4(CH_2)_4$–	70	40	15	0	240	60	83	11.0	17
	140	60	87	4.4	78	20	0	0	8

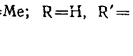
Table 2 reveals no regular variation in toxicity and protective activity on passing from an amino-thiol to the corresponding disulphide: either an increase or a decrease in toxicity, accompanied by an increase, a decrease, or maintenance of the protective activity, may be observed depending on the nature of the substituent.

Kostyukovskii et al.[14] found that increasing the degree of substitution of the amino-groups in cystamine leads to an increase in toxicity, while protection is maintained at the same level. Quaternisation of the nitrogen makes the compound extremely toxic and almost inactive.

$RR'NCH_2CH_2SH$ (XXV)

R = R′ = H; R = H, R′ = Me

$RR'NCH_2CH_2S-SCH_2CH_2NRR'$ (XXVI)

R = R′ = Me; R = H, R′ = 

Tank and Zherebchenko[25] compared the toxicity and the protective activity of several thiol–disulphide pairs such as 2-aminoethanethiol (XXV) and cystamine (XXVI), and found that these properties vary with the species of animal. Thus with mice no relation could be established between the toxicity and antiradiation activity and the thiol or disulphide structure. Experiments on rats showed greater toxicity and a somewhat higher protective efficiency with disulphides than with the corresponding thiols.

$(AcNHCH_2CH_2S-)_2$ (XXVII)

$AcNH-(CH_2)_n-S-S-CH_2CH_2NHC_{10}H_{21}$ (XXVIII)

a $n=2$; b $n=3$

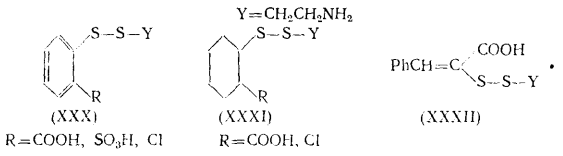
$AcNHCH_2CH_2-S-S-(CH_2)_4-X$ (XXIX)

a $X=SO_3Na$; b $X=SO_2Na$

Field and his coworkers[26-29] have made interesting investigations on the synthesis of symmetrical and unsymmetrical disulphides based on 2-aminoethanethiol and have studied their protective activity. It was discovered that *NN'*-diacetylcystamine (XXVII)[29], like its unsymmetrical analogue (XXVIIIa) having a long *N'*-alkyl substituent[26], does not protect mice from radiation. The homologue of the latter compound with three methylene units between the sulphur atom and the acetamido-group (XXVIIIb) showed a medium protective action[26].

The sulphonate (XXIXa) has a weak protective effect[27], whereas the corresponding sulphinate (XXIXb) proved to be an efficient protective agent. An intraperitoneal dose of the latter sodium salt of 172 mg kg^{-1} (LD_{50} = 800 mg kg^{-1}) protected 93% of mice when destruction of a control group was complete (I_{ip} = 9.0). The degree of protection given by oral introduction of (XXIXb) was also high: a dose of 278 mg kg^{-1} with LD_{50} = 1050 mg kg^{-1} gave 100% survival of the animals (I_{or} = 7.5).

Substances having protective properties have been discovered also among unsymmetrical disulphides of the types[28]

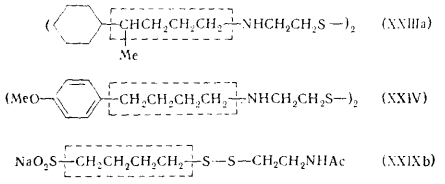


(XXX) R=COOH, SO_3H, Cl

(XXXI) R=COOH, Cl

(XXXII)

It is extremely interesting that the most active disulphides



(XXIIIa)

(XXIV)

(XXIXb)

* Presumably these formulae had originally been numbered (XXXIII)–(XXXV) (Ed. of Translation).

are structurally similar, for they all contain a chain of four carbon atoms. Unfortunately, the lack of data do not allow a reason to be suggested for the role of this factor in the protective effect.

Although less interest has evidently been taken during recent years in disulphides as potential protective agents than in the amino-thiols from which they are derived (a total of ~ 45 such compounds have been studied), highly efficient products have been discovered among them, such as bis-2-*N*-4'-*p*-methoxyphenylbutylaminoethyl disulphide (XXIV) and sodium 4-2'-acetamidoethyldithiobutanesulphinate (XXIXb), the latter showing considerable effectiveness when administered orally. This suggests that the potentialities of 2-aminoethyl disulphides as protective agents are by no means exhausted, and that still more efficient products may be expected to appear in this series.

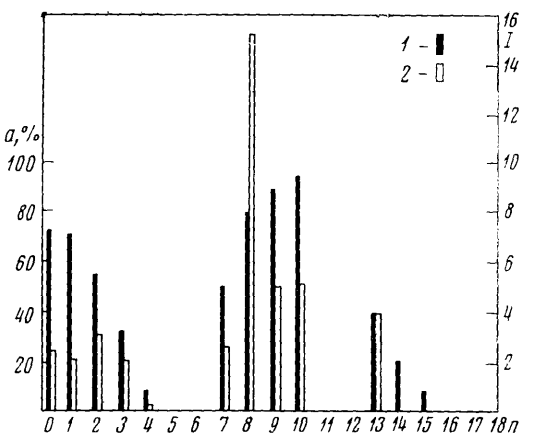
2. *N*-Substituted Aminoethyl Thiosulphates (Bunte's Salts)

In the search for protective agents containing the 2-aminoethanethiol structure the greatest attention has been paid during the past five years to derivatives of aminoethyl thiosulphates, Bunte's salts. The discovery in 1968 of extremely high protective action among these compounds[7] was in effect a turning point in the search for chemical means of protection from ionising radiation.

$H_3\overset{+}{N}CH_2CH_2SSO_3^-$ (XXXVI)

$R\overset{+}{N}H_2CH_2CH_2SSO_3^-$ (XXXVII)

The primogenitor of this series of compounds—2-aminoethyl thiosulphate (XXXVI)—possesses a high protective effect, but in doses which are almost toxic[30]. With LD_{50} = 450 mg kg^{-1} the optimum protective effect of 73% survival was observed with an intraperitoneal dose of 350 mg kg^{-1} in mice. Thus I = 2.2 for (XXXVI): i.e. the compound is relatively inefficient.



Effect of number n of carbon atoms in alkyl group in the compounds $C_nH_{2n+1}N^+H_2.CH_2.CH_2.SSO_3^-$ on: 1) percentage survival of mice a; 2) protective index I.[31]

Klayman et al.[31] studied the prophylactic protective action against radiation of many *N*-alkylated aminoethyl thiosulphates (XXXVII), and discovered an interesting relation between the protective effect and the size of the alkyl group, clearly illustrated by the diagram. Three peaks of activity can be seen, and it is interesting that activity does not always vary in parallel with toxicity. Several Bunte salts containing branched-chain alkyls attached to the nitrogen atom have quite a high protective effect. This is most clearly shown by the 1-methylheptyl derivative (XXXVIII), which in a dose of 75 mg kg^{-1} protects all animals from an absolutely lethal dose of radiation (I_{ip} = 3.7). Among the more than 30 *N*-alkylated

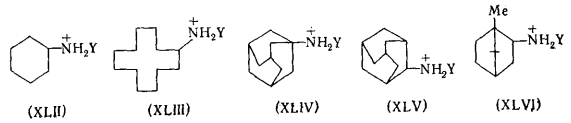
derivatives (XXXVII) studied the most effective protective agent was *N*-octylaminoethyl thiosulphate (XXXIX): at a dosage of 15 mg kg^{-1} with LD_{50} = 125 mg kg^{-1} (intraperitoneal) the survival rate of mice was 80% (I_{ip} = 15.0). Another compound of this series, decylaminoethyl thiosulphate, showed a protective action of ~ 50% at doses of 10–30 mg kg^{-1} in monkeys [32].

$Y{=}CH_2CH_2SSO_3^-$ $C_6H_{13}CH(Me)-\overset{+}{N}H_2-Y$ (XXXVIII) $n-C_8H_{17}-\overset{+}{N}H_2-Y$ (XXXIX)

The encouraging results obtained in the study of *N*-alkylated aminoethyl thiosulphates stimulated an intense search for protective agents among various *N*-substituted derivatives and other amino-thiol compounds. Polymethylene-*NN'*-bisaminoethyl bisthiosulphates (XL) were relatively inactive [12]. A quite well defined protective action was shown by certain compounds containing higher hydroxyalkyl and methoxyalkyl groups (XLI). [7]

$Y{=}CH_2CH_2SSO_3^-$; $Y-\overset{+}{N}H_2-(CH_2)_n-\overset{+}{N}H_2-Y$ (XL) n=6–9 $RO-(CH_2)_n-\overset{+}{N}H_2-Y$ (XLI) R=H, Me; n=4, 7–10

Several workers [7,15,16] have studied the protective properties of Bunte salts having alicyclic substituents in the amino-group. The antiradiation activity of compounds in which the alicyclic substituent is attached directly to the nitrogen atom depends on the size of the ring and the bulk of the substituent. Thus the cyclohexyl derivative (XLII) is inactive [7], whereas the cyclododecyl analogue (XLIII) possesses a moderate protective action [15]; the 1- and 2-adamantyl (XLIV) and (XLV) and the 2-bornyl (XLVI) derivatives are considerably more active [15].



(XLII) (XLIII) (XLIV) (XLV) (XLVI)

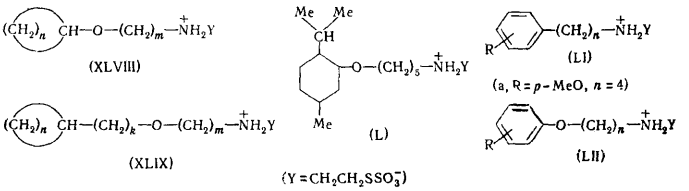
($Y = CH_2CH_2SSO_3^-$)

It was shown for cyclopentane and cyclohexane derivatives that introducing a polymethylene chain between the alicyclic substituent and the nitrogen atom leads to the appearance or enhancement of activity with a diminution in toxicity [7]. The optimum length was pentamethylene. Activity was found among compounds containing four-, five-, six-, and seven-membered rings.

It is interesting that, in a series of derivatives with straight-chain alkyl substituents, maximum efficiency is found with the C_8 group, whereas in cycloalkylalkyl derivatives this occurs in most cases when the substituent contains a total of nine or ten carbon atoms. Branching in the hydrocarbon chain joining the alicycle to the amino-group improves the efficiency of the protective action while having diverse effects on the level of toxicity, as is shown by Table 3 for cyclohexylalkyl derivatives (XLVII). [7]

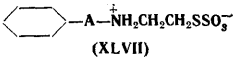
It is worth noting that Westland et al. reported [16] that the *L*-form of *N*-cyclohexylbutylaminoethyl thiosulphate (XLVIIa), while possessing the same toxicity as the racemate, is almost trebly efficient as a protective agent. The laevorotatory isomer has the very high protective index I_{ip} = 30.

Analogues of the above compounds containing an ethereal oxygen atom between the alicycle and the hydrocarbon chain (XLVIII) or in the chain itself (XLIX) also have a protective action against radiation [7,16]. Among them (XLVIII: n = 7; m = 4) [7] and 5'-*L*-menth-3''-yloxypentylaminoethyl thiosulphate (L) [16] are distinguished by their activity, with protective indices I_{ip} of 9.0 and 8.0 respectively.



(XLVIII) (XLIX) (L) (Y = $CH_2CH_2SSO_3^-$) (LI) (a, R = *p*-MeO, n = 4) (LII)

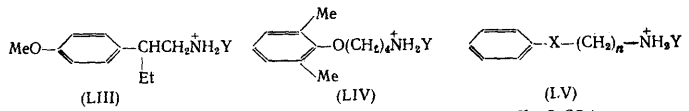
Table 3. Protective properties of cyclohexylalkyl derivatives.



(XLVII)

A	LD_{50}, mmole kg^{-1}	ED, mmole kg^{-1}	Protection, %	I
CH_2	1.36	0.43	20	0
$(CH_2)_2$	0.34	0.19	27	2.3
$(CH_2)_3$	0.58	0.39	86	2.8
$(CH_2)_4$	0.17	0.034	87	9.4
$(CH_2)_5$	0.03	0.015	7	0
$(CH_2)_6$	0.028	0.014	53	3.2
$CHMeCH_2$	0.43	0.18	40	3.4
$CHEtCH_2$ (a) (racemate)	1.00	0.17	80	10.8
$CH(Me)-CH_2CH_2CH_2$	0.25	0.08	100	6.3
$CH(Et)-CH_2CH_2-$	0.48	0.08	60	9.6
$CH_2CH(Et)-CH_2$	0.45	0.048	73	16.3

Equally detailed studies have been made on *N*-arylalkyl (LI) and *N*-aryloxyalkyl (LII) derivatives of aminoethyl thiosulphate [7,17,33]. Among the former type (LI) the most active were the mono- and bis-methoxyphenyl derivatives having n = 4 or 5, and the greatest attention has been attracted to *N*-4'-*p*-methoxyphenylbutylaminoethyl thiosulphate (LIa). A dose of 30 mg kg^{-1} with LD_{50} = 120 mg kg^{-1} gave 87% protection to mice, whereas a control group underwent complete destruction (I_{ip} = 7.5). It is interesting that its isomer (LIII) with the same branched chain as in the most active cyclohexane analogue (XLVIIa) was inactive [17]. Introducing an ethereal oxygen atom between the benzene ring and the polymethylene chain has no significant effect on the toxicity or the protective action of the compounds. The nature of the substituent in the benzene ring is also almost without effect on the activity. Branching in the chain removes the protective action.



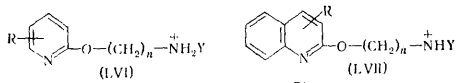
(LIII) (LIV) (LV)

$Y{=}CH_2CH_2SSO_3^-$ (X=S, SO_2)

The most efficient protective agent of this series of compounds is 2''',6'''-dimethylphenoxybutylaminoethyl thiosulphate (LIV). With LD_{50} = 250 mg kg^{-1} a dose of 100 mg kg^{-1} provides 100% protection for mice, and a dose of 25 mg kg^{-1} gives 73% protection. The protective index is I_{ip} = 17.3.

Analogues (LV) of the above compounds in which a sulphur atom or a sulphonyl group has replaced the oxygen

atom in the chain exhibited no appreciable protective action[13].



(LVI) (LVII)

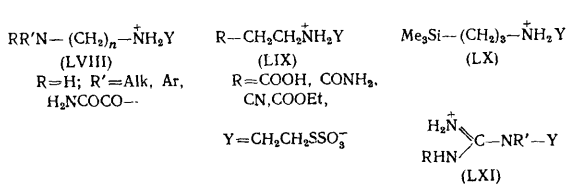
(Y = $CH_2CH_2SSO_3^-$)

Heterocyclic analogues of cycloalkoxy- and aryloxy-alkylated derivatives containing a pyridine (LVI) or a quinoline (LVII) ring have also been synthesised, and their protective action has been studied[8]. The former contained as substituents R halogen, nitro, and cyano at positions 3‴, 5‴, and 6‴, with the number of methylene units varying from 2 to 7. The quinoline derivatives contained methyl, trifluoromethyl, methoxyl, and chlorine in the ring, with 2–6 methylene units. Highly efficient protective agents having a large therapeutic spectrum of action were discovered among compounds of this type (Table 4).

Table 4. Protective properties of pyridine and quinoline derivatives.

Compound	R	n	Dose, mg kg^{-1}		Survival, %	I_{ip}
			LD_{50}	ED		
LVI	5-Br	4	180	100	93	
				50	60	5.8
LVI	5-Br	5	90	25	73	6.2
LVI	5-Cl	5	225	19	87	20.0
LVI	5-Cl	6	120	30	67	6.7
LVI	3,5-Br_2	5	163	25	67	11.0
LVII	H	3	220	25	93	17.0
LVII	4-Me	3	180	25	80	13.4
LVII	4-Me	4	225	50	93	8.7
LVII	6-MeO,4-Me	2	100	12	73	14.4
LVII	4.6-Me_2	3	125	19	93	12.7

By analogy with the thiol derivatives, studies were made on several Bunte salts with an aminoalkyl chain attached to the nitrogen atom (LVIII) and containing the terminal amino-group either unsubstituted[34] or with aryl[20], oxamide[22], or other[21] substituent. However, none of them protected mice from radiation. Several derivatives of 2-aminoethyl thiosulphate containing a propionic-acid residue attached to the nitrogen atom (LIX) were studied[23] and all found to exhibit a weak protective effect against radiation. The trimethylsilylpropyl derivative (LX) was also inactive[19]. Klayman et al.[35] examined several derivatives of guanidylethyl thiosulphate of type (LXI), and found most of them to possess a pronounced protective action. The most active was the derivative in which the nitrogen atoms were unsubstituted (LXI: R = R′ = H): a dose of 100 mg kg^{-1} (LD_{50} = 275 mg kg^{-1}) protected 80% of mice: I_{ip} = 5.0.



(LVIII) R=H; R′=Alk, Ar, H_2NCOCO–

(LIX) R=COOH, $CONH_2$, CN, COOEt,

Y=$CH_2CH_2SSO_3^-$

(LX)

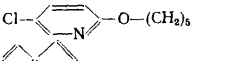
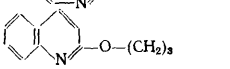
(LXI)

It had been thought earlier that derivatives of aminoethyl thiosulphate had no protective action on mice when given orally. Westland et al.[7,17] disputed this opinion, having discovered moderate activity on the oral introduction of several of the above *N*-cycloalkyl- and *N*-arylalkylated derivatives showing the greatest protective effect on intraperitoneal administration. Oral introduction diminished the toxicity of these compounds by 90–99%, but considerably larger doses were required to achieve a protective effect.

Among the above compounds *N*-*p*-methoxyphenylbutylaminoethyl thiosulphate (LIa) showed the greatest protective action. When introduced 30 min before irradiation, it protected up to 87% of mice; shortening the period to 15 min led to a sharp decrease in the survival of the animals.

The above experimental results for ~ 300 aminoethyl thiosulphate derivatives as protective agents administered intraperitoneally lead to certain conclusions on the effects of the structure of the *N*-substituents on toxicity and protective activity. Alkyl and cycloalkyl-, aryl-, and heteryl-alkyl substituents, in several cases with some increase in toxicity, led to an appreciable decrease in the protective dose and thereby widened the therapeutic spectrum. The optimum structure in this series must evidently be regarded as that in which the *N*-substituent in the aminoethyl thiosulphate contains 8–12 carbon atoms, one or two of which may be replaced by nitrogen or oxygen atoms. If the substituent is not purely aliphatic, the number of methylene groups joining the cyclic fragment to the amino-group should be 3–5.

Table 5. Protective properties of R–$N^+H_2CH_2CH_2SSO_3^-$.

R	Doses				I_{ip}	Ref.
	LD_{50},		Ed,			
	mmoles kg^{-1}	rel. to XXXVI	mmoles kg^{-1}	rel. to XXXVI		
H (XXXVI)	2.9	1	2.2	1	2.2	30
n-C_8H_{17}	0.46	0.16	0.056	0.025	15.0	31
cyclo-C_6H_{11}–CH (Et) * – $(CH_2)_2$	1.00	0.36	0.060	0.027	30.0	16
p-$MeOC_6H_4$–$(CH_2)_4$	0.77	0.25	0.093	0.042	7.5	17
	0.64	0.22	0.053	0.024	20.0	8
	0.65	0.22	0.047	0.021	17.0	8

* *L*(–)-isomer.

Table 5 gives comparative data for the most efficient protective agents—*N*-substituted aminoethyl thiosulphates—which clearly demonstrate the advantage of these compounds over their primogenitor—2-aminoethyl thiosulphate itself. The protective efficiency of such compounds is evidently determined not so much by the length of the group, which may influence the surface-active properties of the compounds, as by the "weight" of the substituent (around 100–200), its configuration, and other factors. The broadened therapeutic latitude in these substances must be attributed to "dilution of the active fragment" by the increase in molecular weight. Table 5 shows that introducing a substituent increases the toxicity by factors 3–6 but at the same time diminishes the effective protective dose to a still greater extent, by factors of 20–40.

3. Derivatives of *S*-2-Aminoethyl Dihydrogen Phosphorothiolate

The first member of this series—*S*-2-aminoethyl dihydrogen thiophosphate (LXII)—whose sodium salt has since been termed Cystaphos, was first described in 1961 as an effective protection against radiation[36]. Cystaphos and its simple derivatives were shown to possess quite low toxicity while being highly active[36,37]. Thus with LD_{50} = 930 mg kg^{-1} Cystaphos itself in a dose of 400 mg kg^{-1} protects 95% of mice from an absolutely lethal dose of radiation[36]: i.e. its I_{ip} = 4.5. These were high values for the 1960s, and this series of compounds might have been expected to engross the attention of research workers. However, the literature indicates that fewer aminoethyl thiophosphates than thiosulphates and even thiols have been studied during the past five or six years as potential protection against radiation.

$H_2NCH_2CH_2SPO_3H_2$ (LXII) $RHNCH_2CH_2SPO_3H_2$ (LXIII)

The further search in this series for more efficient protective agents than Cystaphos was directed at complicating the molecule by introducing various hydrocarbon and other groups at the nitrogen atom. Most of the compounds synthesised were isolated and used as the sodium and other salts (formulae in the text will be given for the dihydrogen esters). More than 40 compounds of type (LXIII) have been described containing various substituents—alkyl, carboxyalkyl, carbamoylalkyl, etc.[38]—but data are not given on their protective activity against radiation.

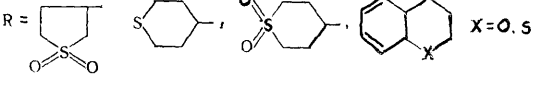
$YHN-(CH_2)_n-NHY$ (LXIV), n=7–10

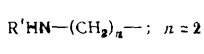
$Y=CH_2CH_2SPO_3H_2$; $YHN-(CH_2)_n-C_6H_{10}-(CH_2)_n-NHY$ (LXV), n=0,1

Some activity has been found with the polymethylenebisaminoethyl bisthiophosphoric esters (LXIV) and their *cis*- and *trans*-cyclohexane analogues (LXV).[12] Replacing an amino-hydrogen atom by bornyl and norbornyl groups diminishes the protective effect found in Cystaphos[15]. The adamant-1-yl derivative (LXVI), although more toxic, gave protection in a smaller dose: with LD_{50} = 560 mg kg^{-1} a dose of 80 mg kg^{-1} showed a protective effect of ~ 80% (I_{ip} = 12.5).[15] Weak protection or none at all was shown by compounds having a heterocyclic *N*-substituent (LXVII)[15] and by the *N*-phenoxy-, *N*-phenylthio-, and *N*-phenylsulphonyl-alkylaminoethyl esters (LXVIII)[13].

$R-HNCH_2CH_2SPO_3H_2$

(LXVI) R = 

(LXVII) R =  X=O, S

(LXVIII) R =  $X-(CH_2)_n-$, X = O, S, SO_2; n = 2, 3

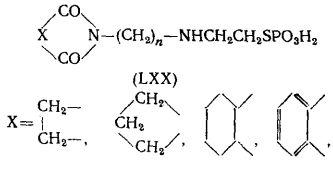
(LXIX) $R = R'HN-(CH_2)_n-$; n = 2–6

Attention was directed mainly at seeking protective agents among *N*-aminoalkyl derivatives of the *S*-aminoethyl thiophosphate (LXIX)[20,21,34]. Introduction of an aminoalkyl chain of 2–6 units terminating in a free amino-group (R′ = H) produces a significant increase in protective efficiency above that of Cystaphos[34]. All *N*-aminoalkyl derivatives other than the first member of the series (LXIX: R′ = H, n = 2) are more toxic than Cystaphos but protect animals in considerably smaller doses. Table 6 shows that most of them have protective indices exceeding that of Cystaphos by about 50%. The protective activity of certain compounds of type (LXIX) is maintained when a hydrogen atom of the terminal amino-group is replaced by methyl or ethyl (R′ = CH_3, C_2H_5); the introduction of an octyl or a cyclohexyl substituent (R′ = C_8H_{17}, C_6H_{11}) deprives the compound of activity[20]. The *N*-aminopropylaminoethyl ester (LXIX: R′ = H, n = 3)—known by the number WR-2721 or the name Gammafos—has been subjected to a more thorough and detailed study as a potential protective agent[39–42]. These investigations enabled the advantage of this agent over Cystaphos to be shown up more boldly.

Table 6. Protective properties of derivatives of (LXIX).

LXIX R′	n	Doses, mg kg^{-1}		Protection, %	I_{ip}
		LD_{50}	ED		
Cystaphos		930	400	95	4.5
H	2	1300	400	100	6.5
H	3	700	300	86	4.3
H	4	800	200	80	7.2
H	5	550	150	100	7.3
H	6	550	150	93	7.1
Me	3	800	200	87	
			100	46	11.7

Various *N*-imidoalkyl derivatives of the aminoethyl ester (LXX) (formed from the imides of succinic, glutaric, cyclohexane-1,2-dicarboxylic, and phthalic acids) have been studied in the search for more effective compounds[21,43,44]. Most of these compounds showed weak or moderate action against radiation. The most active was the cyclohexane derivative, which gave protection even when administered through the mouth[44].



(LXX)

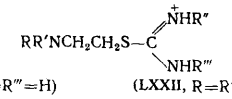
X= n=2–4

The above discussion can be summed up in the conclusion that, among the > 100 *N*-substituted aminoethyl dihydrogen thiophosphates described during the past six years, the most effective protective agents were the adamant-1′-yl (LXVI) and methylaminopropyl (LXIX: R′ = CH_3, n = 3) derivatives, with protective indices reaching ~ 12.

4. Aminoethylthiouronium Derivatives

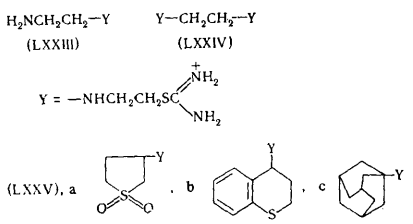
The search for protective agents has been considerably less intense among aminoethylthiouronium derivatives (LXXI), which, while possessing a high protective action, is itself an extremely toxic substance (I = 1.5–2.0). Japanese workers[45,46] examined systematically all possible

N-methyl derivatives (LXXII), but gave no data on their biological activity.

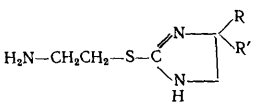


(LXXI, R=R′=R″=R‴=H) (LXXII, R=R′=R″=R‴=Me, H)

The aminoethyl derivatives (LXXIII) and (LXXIV) are inferior in protective activity[47] to the original aminoethylthiouronium.



Elliott and his coworkers[15] discovered that derivatives of (LXXI) having heterocyclic residues such as dioxothiophanyl and thiachromanyl attached to the chain nitrogen atom (LXXVa, b) possess no protective activity, whereas the adamant-1′-yl analogue (LXXVc) develops some action.



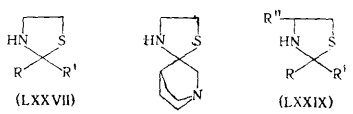
(LXXVI)

(R=R′=H; R=R′= Alk, cycloAlk)

Derivatives of (LXXI) have been synthesised with amino-acid and dipeptide residues in the thiouronium group[48], but, like the cyclic analogue (LXXVI)[47,49], these compounds were inferior to aminoethylthiouronium itself in protective activity against radiation.

5. Thiazolidines

Increasing interest has been taken during recent years in thiazolidines, cyclic analogues of 2-aminoethanethiol. The search for protective agents was continued in the traditional direction—among 2-substituted thiazolidines (LXXVII), which are usually regarded as a long lasting, less toxic form of aminoethanethiol because of their ability to break down gradually in the organism with liberation of the latter product. Among compounds of this type studied, several exhibited moderate protective activity—unsubstituted thiazolidine (LXXVIIa), the 2-alkyl and 2-aryl[50], also the 2,2-dimethyl (LXXVIIb) and 2-trichloromethyl (LXXVIIc) derivatives[51], and 2,2-spiroquinuclidylthiazolidine (LXXVIII)[52].

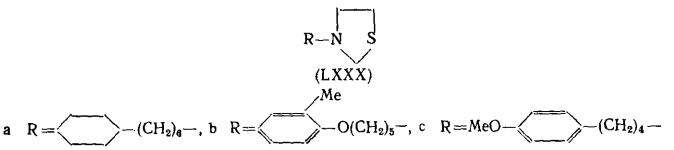


(LXXVII) (LXXVIII) (LXXIX)

a R=R′=H;
b R=R′=Me;
c R=H, R′=CCl_3;
d R=Me, Pr, Ph; R′=COOEt;
e R=Me, Pr, Ph; R′=CH(CH_2Ph)COOEt

a R=R″=H, R′=$COOR^{III}$ (R^{III}=H, C_1-C_{18});
b R=H, R′=$COOR^{III}$ (R^{III}=H, C_1-C_{18}), R″=$COOR^{III}$ (R^{III}=H, Me);
c R=Me, R′=Et, R″=COOH

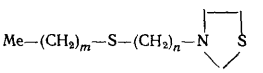
Yakovlev et al.[53] have shown that 2-glycosyl derivatives of thiazolidine protect yeast cells and *Escherichia coli* from the action of ionising radiation. Thiazolidine-2-carboxylic and -2,4-dicarboxylic acids and esters (LXXIXa, b), obtained by condensing glyoxylic acid and its esters with 2-aminoethanethiol and cysteine respectively[54,55], showed slight protective activity, as did compounds containing acetic-ester residues at position 2 (LXXVIId, e).[56] Among 2,2-dialkylthiazolidine-4-carboxylic acids a protective effect was observed only in (LXXIXc)[57]; 5,5-dimethylthiazolidine-4-carboxylic acid—a cyclic analogue of penicillamine—was inactive[51].



(LXXX)

a R=, b R=, c R=MeO-

The most important and interesting results were obtained in a study of the protective properties of *N*-substituted thiazolidines (LXXX). Westland et al.[16] investigated the action against radiation of fifteen 3-cycloalkylalkyl- and 3-aryloxyalkyl-thiazolidines. Several of them showed moderate activity, e.g. 3-6′-cyclohexylhexyl- and 3-5′-*o*-tolyloxypentyl-thiazolidines (LXXXa, b), whose protective indices were respectively 6.0 and 8.0. As among the amino-thiol derivatives containing an *N*-*p*-methoxyphenylalkyl substituent[17], only 3-4′-*p*-methoxyphenylbutylthiazolidine (LXXXc) showed sufficiently high protection, with I_{ip} = 7. Compounds with a branched polymethylene chain or with a 2-methyl group in the thiazolidine ring were devoid of activity. The thiazolidine derivative (LXXXc) gave weak protection when administered through the mouth.

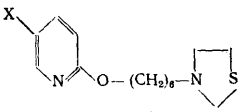


(LXXXI)

m=0–8, *n*=2–7

a *m*=5, *n*=6; b *m*=3, *n*=7; c *m*=4, *n*=5; d *m*=5, *n*=5

Most of the 3-alkylthioalkylthiazolidines (LXXXI) studied (> 25) afforded weak or no protection to irradiated mice on intraperitoneal administration, and only two compounds (a and b) had a moderately protective effect[58]. Oral introduction gave similar results, but (LXXXIa) protected weakly, then (LXXXIb). Furthermore, compounds (LXXXIc, d), relatively inactive on intraperitoneal administration, proved to be efficient when given orally: thus an oral dose of (LXXXIc) of 125 mg kg^{-1}, with LD_{50} = 650 mg kg^{-1}, protected 92% of mice, and its protective index was I_{or} = 10.



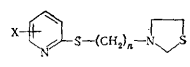
(LXXXII)

a X=5-Cl, b X=5-I

In contrast to pyrid-2″- and quinol-2″-yloxyalkylaminoethyl thiosulphates, among which protective agents of high efficiency on intraperitoneal introduction were discovered, their thiazolidine analogues (> 50 studied) were almost inactive with this method of administration[8]. However, two of them—3-6″-5‴-chloro- and 3-6″-5‴-iodo-pyrid-2‴-yloxyhexylthiazolidines (LXXXIIa, b)—were quite effective on oral administration, with protective indices respectively of ~ 7.0 and 6.0.

Compounds providing efficient protection on oral introduction were discovered also among 3-halogenopyrid-2'''-ylthioalkylthiazolidines (LXXXIII)[56] containing 3–10 methylene groups. The most active of them afforded no protection on intraperitoneal introduction (Table 7).

Table 7. Protective properties of the derivatives.



(LXXXIII)

X	n	Intraperitoneal administration				Oral administration			
		doses, mg kg^{-1}		survival, %	I_{or}	doses, mg kg^{-1}		survival, %	I_{or}
		LD_{50}	ED			LD_{50}	ED		
5-Br	5	275	100	93	5.3	800	200	73	6.9
5-Cl	7	56	30	20	0	650	75	60	14.0
5-Cl	8	125	70	8	0	500	125	80	7.2
3,5-Cl_2	7	275	125	60	3.5	1000	800	0	0

Thus quite efficient protective agents, which develop their activity predominantly on oral introduction, have been discovered among the > 140 thiazolidine derivatives studied, primarily among those substituted on the nitrogen atom. These results may provide some support for the hypothesis that thiazolidine compounds may act as long lasting forms of the corresponding 2-aminoethanethiol derivatives. However, it is still difficult, on the basis of existing data, to reach conclusions on the general effects of substituents in the thiazolidine ring on the protective action of these compounds and on differences in activity between intraperitoneal and oral administration.

6. 2-Aminoethanethiol Derivatives modified in the Hydrocarbon Chain

The structure of 2-aminoethanethiol—the primogenitor of protective agents—can be varied, not only by substitution at the amino and thiol groups, but also by modification of the hydrocarbon chain. Early studies had been made[3,59] of the effect of chain lengthening and branching on the protective activity. These investigations have recently been continued, and novel, more radical changes have been made in this part of the molecule.

$H_2N-(CH_2)_n-SX$ a X=H, n=2,6; b X=SO_3H, n=3,6–10;
(LXXXIV) c X=PO_3H_2, n=3

$H_2N-(CH_2)_m-NH-(CH_2)_n-SPO_3H_2$
(LXXXV)

A decrease in the protective effect until it completely disappears is confirmed on passing from the two-unit (ethylenic) chain in 2-aminoethanethiol to chains of three to six units (LXXXIVa)[60]. A similar rule is observed for the aminoalkyl thiosulphates (LXXXIVb)[15,30]. A sharp drop in protective activity is found also in the trimethylene analogue of Cystaphos (LXXXIVc)[34].

A rather different rule is found in *N*-aminoalkylaminoalkyl phosphorothiolates (LXXXV)[34]. Depending on the length m of the polymethylene chain in the substituent, increase in the distance between the sulphur and nitrogen atoms from two to three methylene units may either enhance or diminish the protective efficiency (Table 8).

The compound (LXXXV: $n = m = 3$) is one of the most efficient protective agents among derivatives of aminoalkyl phosphorothiolates.

Gandacek and Swartz[61] tried to discover a connection between the protective activity of amino-thiols and the possibility of intramolecular hydrogen bonding between the nitrogen and sulphur atoms. They showed that such a bond can be formed only in the first member of the series, 2-aminoethanethiol, which in the crystalline state has the gauche conformation. In their view, however, it is improbable that this fact will be significant in the establishment of a protective effect, since the conformation will certainly change under physiological conditions—in solution.

$H_2N-CHCH_2S-X$ (LXXXVI)
Me

H_2N-CH_2CHS-X (LXXXVII)
Me

a X=SO_3H, b X=H

Table 8. Protective properties of derivatives (LXXXV).

LXXXV, m	n = 2				n = 3			
	doses, mg kg^{-1}		survival, %	I_{ip}	doses, mg kg^{-1}		survival, %	I_{ip}
	LD_{50}	ED			LD_{50}	ED		
2	1300	400	100	6.5	1300	500	100	5.2
3	700	300	86	4.3	560	75	80	13.5
4	800	200	80	7.2	225	100	13	0

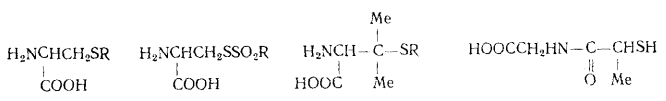
Investigations have continued during recent years on the effect of branching in the ethylene chain in compounds having the 2-aminoethanethiol structure on their toxicity and protective activity. Attachment of a methyl group to the carbon atom adjacent to the nitrogen atom in *S*-aminoethyl thiosulphate (LXXXVIa) maintains both activity and toxicity, whereas the isomer having the methyl group attached to the carbon adjacent to the sulphur atom (LXXXVIIa) is considerably less toxic, but completely devoid of protective action. It is interesting that the opposite relation is observed with the two analogous amino-thiols (LXXXVIb) and (LXXXVIIb)[30]. The trimethylene analogue of aminoethylthiouronium and certain derivatives substituted on the second carbon atom were less active than itself[62].

$H_2NCH_2CHCH_2-S-C(=\overset{+}{N}H_2)-NH_2$
R
(LXXXVIII)
R=H, OH, Cl, Br

$H_2N-(CH_2)_3-NH-CRR'-CH_2S-X$
(LXXXIX)
X=H, SO_3H, PO_3H_2

Detailed study of the effect of methylating the carbon atom adjacent to the nitrogen atom in the compounds (LXXXIX) on their protective activity and toxicity revealed no general rule[34]. Introducing a single methyl group into these compounds with X = H, SO_3H hardly affects the toxicity or activity, whereas when X = PO_3H_2 it increases the toxicity and decreases the activity. Replacing a second hydrogen atom by methyl leads to a sharp increase in toxicity and loss of activity when X = H; with X = SO_3H, PO_3H_2, however, the toxicity diminishes, while the

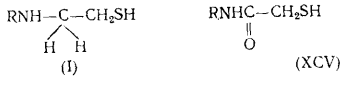
Bunte salt remains inactive, whereas the phosphorothiolate becomes even more effective than the first member of the series (R = R′ = H).



(XC, R=H) (XCI, R=SO_3H) (XCII) R=Me, *p*-MeC_6H_4 (XCIII) a R=$MeSO_2$ (XCIV) (Thiola)

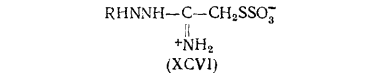
The search for protective agents has continued among derivatives of cysteine (XC), which was the first to protect animals from ionising radiation[3]. Japanese workers[63] made a detailed study of the antiradiation action of the ethyl ester, administered both intraperitoneally and orally. This relatively non-toxic compound was similar to cysteine in protective action, but did not protect mice from an absolutely lethal dose of radiation. The Bunte salt (XCI) was less active than cysteine itself[30]. Among the more complicated derivatives (XCII)[64] and (XCIII)[65], moderate protective activity was shown only by (XCIIIa).

Interesting results have been obtained during recent years from more fundamental changes in the hydrocarbon chain of amino-thiols. Sugahara et al.[66,67] discovered that α′-mercaptopropionylglycine (XCIV), which they termed "Thiola", while being relatively non-toxic (intraperitoneal LD_{50} = 2000 mg kg^{-1}), has an effect against radiation when small doses (20–40 mg kg^{-1}) are given in experiments on mice. However, it protects animals only at radiation doses leading to destruction of at most 70% in a control group. According to these workers[67] Thiola exerts a curative effect, both with parenteral and with oral application, on humans subjected X-radiotherapy: chromosome breakages in leucocytes become fewer after administration of this preparation. A Swedish patent[68] described the production not only of Thiola but also of several other derivatives of this type.



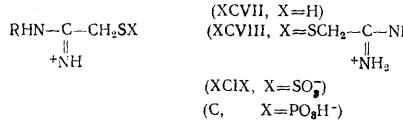
(I) (XCV)

The above work continued earlier investigations of the protective action of mercaptoacetamides (XCV)[69,70], which can be regarded as derived from 2-aminoethanethiol (I) in which the methylene adjacent to the nitrogen atom has been replaced by a carbonyl group. In 1969 Fridinger and Robertson[71] published a study of the protective action of four substituted acetamidrazone thiosulphates (XCVI). They provided weak protection from radiation for mice. It is readily seen that these compounds can be regarded as having the same type of modification of the ethylene chain: two hydrogen atoms have now been replaced not by carbonyl but by the isosteric imino-group.



(XCVI)
R=*p*-$NO_2C_6H_4$, *o*-MeC_6H_4, *p*-FC_6H_4, $EtOOCCH_2$

This latter work was probably the origin of studies by American workers headed by Westland[72] on the protective activity of 84 derivatives of mercaptoacetamidine (XCVII) and its *S*-functional substitution products—disulphides (XCVIII), thiosulphates (XCIX), and phosphorothiolates (C)—with various substituents attached to the nitrogen atom.



(XCVII, X=H) (XCVIII, X=SCH_2—C(=$^+NH_2$)—NHR) (XCIX, X=SO_3^-) (C, X=PO_3H^-)

The simplest compounds of this type—mercaptoacetamidines (XCVII)—far exceeding the corresponding aminoethanethiols in toxicity, were quite effective both with intraperitoneal and with oral administration. The most active among them was the compound with a free amino-group (XCVIIa: X = H), as well as the adamant-1-ylmethyl and 3,5-dimethyladamant-1-ylmethyl derivatives (XCVIIb, c). It is interesting that they were more effective when administered orally (Table 9). The distance of the bulky adamantyl group from the amidine nitrogen atom had little effect on the activity.

The oxidised forms of the mercaptoacetamidines—the corresponding disulphides (XCVIII)—are somewhat inferior in efficiency on intraperitoneal administration, but rather better when introduced orally. Data on the most efficient compounds of this series—the *N*-unsubstituted disulphide (XCVIIIa), adamant-1-ylmethyl, 3,5-dimethyladamant-1-ylmethyl, and cycloheptylmethyl derivatives (XCVIIIb–d)—are included in Table 9. It is noteworthy that the adamantyl derivatives are inactive on intraperitoneal administration. The compound (XCVIIIb) is the most effective of all known oral protective agents studied on mice: its therapeutic index is ~ 13, and its protective index ~ 20.

The largest group among the compounds studied (56) comprised the Bunte salts (XCIX) with cycloalkyl-, aryl-, heteryl-, and hydroxy-alkyl substituents attached to the nitrogen atom. Most of them were considerably more toxic than the corresponding aminoethyl thiosulphates, and had a medium and low protective effect. Only three compounds—the 3′,4′-dimethoxyphenylethyl, indol-3′-ylethyl-, and *cis*-2-myrtanyl-acetamidine thiosulphates (XCIXe–g)—showed high efficiency as intraperitoneal protective agents (Table 9). It is interesting that the immediate homologue of (XCIXf), with three methylene groups between the indole ring and the nitrogen atom, is completely inactive. The vast majority of Bunte salts studied did not protect mice from radiation when given orally, and only one compound—the *N*-born-2-yl derivative (XCIXh)—showed a fairly high protective effect with this mode of introduction.

The paper[72] gives results for only four guanylmethyl phosphorothiolates (C). Three of them—the unsubstituted compound (Ca), cycloheptylmethyl (Cd), and cyclooctylmethyl derivatives—exhibit slight protective activity with both methods of administration. Unique behaviour was exhibited by *S*-N^1-3′,5′-dimethyladamant-1′-ylmethylguanylmethyl dihydrogen phosphorothiolate (Cc), which under the experimental conditions was considerably more efficient than all known protective agents on intraperitoneal introduction (Table 9): its therapeutic index exceeded 30, and its protective index was $I_{ip} \simeq 50$. Its protective effect was not so high when used orally.

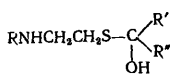
Comparison of the most efficient protective agents of acetamidine structure indicates that activity is increased by the introduction of the bulky adamantyl group attached to the nitrogen atom by a single methylene unit. However, no general rules could be derived for the influence of substituents in the amidino-group or of various functional

Table 9. Protective properties of the derivatives

$RHN-C(=NH_2^+)-CH_2SX$

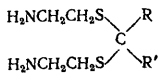
R	X	Compound	Intraperitoneal				Oral			
			doses, mg kg^{-1}		survival, %	I_{ip}	doses, mg kg^{-1}		survival, %	I_{or}
			LD_{50}	ED			LD_{50}	ED		
H	H	XCVII a	52	12	73	7.5	150	20	67	12.5
	disulphide	XCVIII a	60	12.5	100	9.6	125	25	67	8.9
	SO_3^-	XCIX a	87	50	100	3.5	300	100	73	5.2
	PO_3H^-	C a	100	37.5	93	6.0	135	37.5	73	6.2
	H	XCVII b	22	6	67	6.0	65	15	93	8.6
	disulphide	XCVIII b	100	50	7	0	325	25	53	20.0
	SO_3^-	XCIX b	25	10	93	4.8	300	200	0	0
	H	XCVII c	10	5	64	3.3	175	25	80	12.5
	disulphide	XCVIII c	5	3	40	0	250	25	53	15.3
	SO_3^-	XCIX c	44	15	27		600	600	7	0
	PO_3H^-	C c	125	8	93	0				
				4	60	50	425	100	100	15
	disulphide	XCVIII d	22	5	70	7.5	188	25	73	13.0
	PO_3H	C d	38	20	70	2.9	40	20	60	3.2
3,4-$(MeO)_2C_6H_3(CH_2)_2$	SO_3^-	XCIX e	250	50	60	8.0	900	600	0	0
Indol-3'-ylethyl	SO_3^-	XCIX f	180	14	67	21.5	600	500	0	0
cis-Myrtan-2-yl	SO_3^-	XCIX g	63	8	67	13.0	380	200	20	0
Born-2'-yl	SO_3^-	XCIX h	30	15	93	3.9	225	50	87	8.4

derivatives involving substitution at the sulphur atom. The data cited here demonstrate that the most efficient protective agents in experiments with both intraperitoneal and oral introduction into mice occur among compounds of mercaptoacetamidine structure.



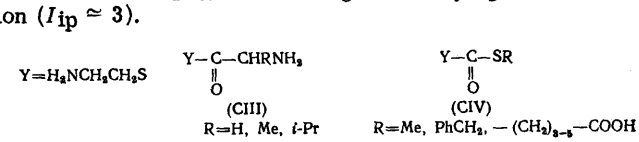
(CI)

R=H, Ac; R'=H, CF_3; R''=CCl_3, CBr_3, CF_3
a R=R'=H, R''=CCl_3; b R=R'=H, R''=COOR''' (R'''=C_1–C_{18}); c R=R'=H, R''=COOMe



(CII)

A few other groups of 2-aminoethanethiol derivatives, differing significantly in structure from the above, have been studied as protective agents. This applies primarily to products formed by reaction with carbonyl compounds. Field et al.[73] studied a series of monothiohemiacetals (CI), and found that one of them (CIa) developed a strong protective action, but in doses close to toxic. French workers[54,55] discovered an extremely efficient protective agent—the hydrochloride of methyl *S*-2'-aminoethylthioglycollate (CIc)—among a large number of condensation products (CIb) of aminoethanethiol with glyoxylic esters. In its prophylactic protective effect in an intraperitoneal dose of 450 mg kg^{-1} ($\frac{1}{2}LD_{50}$) it surpasses 2-aminoethanethiol and aminoethylthiouronium, while being considerably less toxic. Among mercaptals (CII)[51] a single compound (R = R' = $COOC_2H_5$) showed slight activity against radiation ($I_{ip} \simeq 3$).



Y=$H_2NCH_2CH_2S$

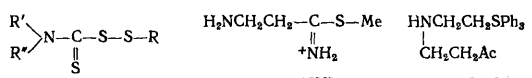
(CIII)

R=H, Me, *i*-Pr

(CIV)

R=Me, $PhCH_2$, $-(CH_2)_{3-5}-COOH$

Rachinskii et al.[74] prepared and studied the protective action of several aminoethanethiol derivatives (CIII) *S*-acylated by amino-acids—glycine, alanine, leucine, etc.—which were less toxic than aminoethanethiol but exhibited the same protective effect in considerably larger doses. The dithiocarbonates (CIV) were relatively ineffective[75], and trithiocarbonates (CV) showed no activity[76].



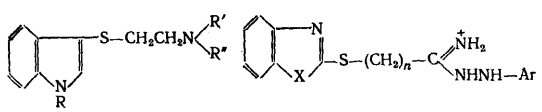
(CV)

R=CH_2CH_2NHAc;
R'=R''=H, Me

(CVI)

(CVII)

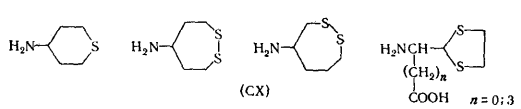
A slight protective effect was shown by the thioimidic ester (CVI)[77] and by the *S*-triphenylmethyl derivative (CVII)[23], for the latter of which a prolonged protective action was assumed. A few *S*-indol-3'-yl derivatives of the type (CVIII) have been synthesised in which R = R' = R'' = H or CH_3, but no results are reported for the protective activity[78].



(CVIII)

(CIX)
X=S, NH; n=1, 2

Interesting investigations were made by Pantev et al.[79,80] in a search for protective agents among *S*-benzazol-2'-ylthioalkanoamidrazones (CIX). The most active was the benzimidazole derivative (CIX: X = NH, n = 2, Ar = *p*-$CH_3C_6H_4$): a dose of 120 mg kg^{-1} protected 56% of mice.



(CX)

a b c d

n = 0; 3

Several cyclic analogues of amino-thiols with one or two sulphur atoms in the ring (CXa–d) were studied[18,81,82], and all proved to be inactive.

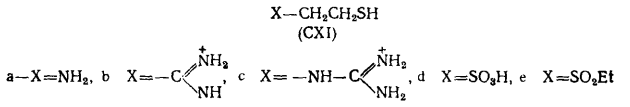
Thus the most efficient protective agents for intraperitoneal and/or oral use under experimental conditions have been found among the almost 150 compounds of amino-thiol structure and having a modified hydrocarbon chain that have been studied.

The information surveyed above shows that more than 900 compounds of amino-thiol structure have been studied during recent years, and among them several highly efficient protective agents under experimental conditions have been discovered. A characteristic feature of the chemical structure of most of them is the presence of a cycloalkyl, adamantyl, aryl, or pyridyl substituent attached to the nitrogen atom through an alkyl, oxyalkyl, or thioalkyl chain.

No data or hypotheses have been published on the role of these structural factors in the development of protection from radiation. The presence of a sufficiently heavy, bulky substituent, usually containing 9–13 carbon atoms, may be supposed to strengthen intermolecular interactions and steric effects and to change the conditions of fixation of such compounds in cells and tissues of the living organism, which will undoubtedly influence the permeability to, the transport, and the distribution of these substances. All this evidently leads in aggregate to an increase in the biological activity of such compounds, when the decrease in the effective protective dose is usually greater than that in the toxic dose (e.g. LD_{50}), which increases the interval between them, i.e. the therapeutic latitude of these substances.

With regard to the thiol function in protective agents of this type, the phosphorothiolate and the disulphide groups must be regarded as optimal for intraperitoneal introduction, and the disulphide and thiazolidine groups for oral administration.

An extremely promising line of research has been fundamental modification of the hydrocarbon chain. The most efficient protective agents have been found among compounds of this type—*S*-N^1-3′,5′-dimethyladamant-1′-ylmethylguanylmethyl dihydrogen phosphorothiolate (Cc) on intraperitoneal administration and bis-N^1-adamant-1′-ylmethylguanylmethyl disulphide (XCVIIIb) when given orally.

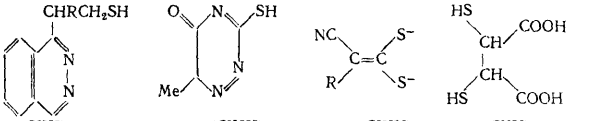


All the results that have accumulated during recent years compel us to change our existing view[3] that the presence of a free amino-group is a necessary condition for the development of high protective activity in compounds having an amino-thiol structure. Kostyukovskii et al.[83] have recently shown that the amino-group in 2-aminoethanethiol (CXIa) can be replaced by several other electron-accepting groups—e.g. amidino, guanidino, sulpho, and sulphonyl (CXIb–e)—without a significant decrease in protective activity. These authors concluded that the protective activity of compounds of type (CXI) is due to the reactivity of the mercapto-group, which can be represented quantitatively by the dissociation constant K_a^{SH}: effective compounds with this structure should have pK_a^{SH} = 7.7–8.7 (the value of this exponent for 2-aminoethanethiol is 8.2).

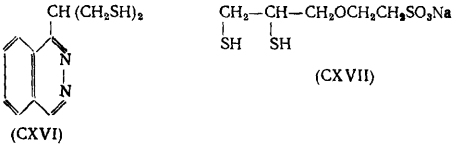
The information in the following Section may serve to confirm that the presence of an amino-group or other nitrogen-containing function is not necessary for the development of a high protective effect, not only in the aminoethanethiol type of compound but also in sulphur-containing compounds in general.

III. OTHER SULPHUR-CONTAINING COMPOUNDS

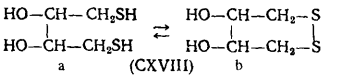
Protective agents have been found during recent years among sulphur-containing compounds of non-aminothiol structure—thiols, thiosulphates, sulphides, di- and trisulphides, dithiocarboxylic acid derivatives, sulphoxides, sulphones, etc.



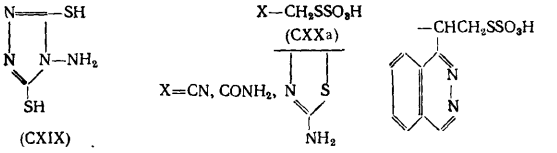
Mercaptoalkyl derivatives of phthalazine (CXII) exhibit slight protective activity[84]. The 5,6-dihydro-3-mercapto-5-oxotriazine (CXIII) is moderately protective[85].



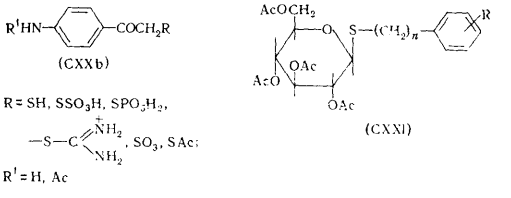
Several studies have been made of the action of various dithiols against radiation. Foye showed[86] that, in contrast to the inactive dimercaptomethylenemalononitrile (CXIVa), the unsaturated mononitriles (CXIVb, c) develop appreciable protective activity. A slight increase in the survival rate of irradiated mice was produced by the prophylactic administration of racemic dimercaptosuccinic acid and its *meso*-form (CXV)[87]. A comparatively slight protective effect was observed with the dithiols (CXVI)[84] and (CXVII)[88].



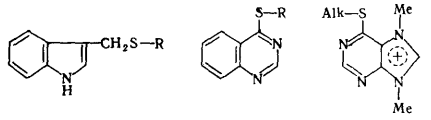
The attention of radiobiologists has been attracted during recent years to dithiothreitol (CXVIIIa)[89–92], which exists in the less toxic[90] cyclic form (CXVIIIb). It was relatively ineffective as a protective agent. Better results were obtained by its medicinal use under the experimental conditions. The *D*-isomer is more active than the *L*-form[91]. The di-*O*-acetyl derivative of (CXVIII) has a weak protective action[92].



Some increase in the survival rate of irradiated mice was observed when the aminotriazoledithiol (CXIX) was used[93].



No activity has been discovered among various types of compounds (CXXa) containing a thiosulphuric acid residue[30,79,84]. Kostyukovskii et al.[94] showed that, in a series of *p*-aminobenzoylmethanethiol derivatives (CXXb), a pronounced protective action was exerted by the phosphorothiolate and the compound containing an *S*-acetyl group.



(CXXII) (CXXIII) (CXXIV)

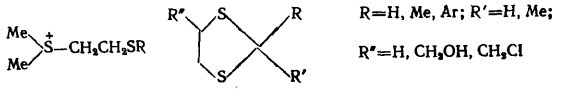
Several compounds of sulphide structure have been studied. Ishiguro et al.[95] found moderate protective action in certain thioglycosides of type (CXXI), of which the most active had R = H and n = 1, 2. In the search for protective agents several sulphides were synthesised with heterocyclic and aryl groups of the types (CXXII)–(CXXIV)[96-98].



R, R' = H, Me, , Ph;
R'' = H, CH_2Cl

(CXXV) (CXXVI)

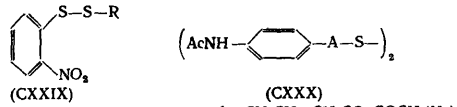
Thien-2-ylmethanol (CXXV), a cyclic analogue of mercaptoethanol, can be included formally among sulphides. A freshly prepared specimen has a weak protective action[99], but after standing for 1 month or exposure to a 1000-W lamp for 18 h this substance shows a fairly strong protective effect. It was assumed[99] that polymerisation occurred under these conditions. Bitoun et al.[100] prepared 13 cyclic analogues of mercaptoethanol of a different type: among these oxathiolans (CXXVI) only the 2,2-dimethyl, 5-chloro-2,2-dimethyl, and spirocyclohexane derivatives exhibited a protective effect of 20–50% on mice.



R=H, Me, Ar; R'=H, Me;
R''=H, CH_2OH, CH_2Cl

(CXXVII) (CXXVIII)
R=H, Ac

Prophylactic introduction of ethane-1,2-dithiol derivatives (CXXVII) produced a slight increase in survival rate of irradiated mice[14]. A detailed investigation of the protective properties of > 30 dithiolans (CXXVIII)—cyclic analogues of ethane-1,2-dithiol—has shown[101] that they include compounds that ensure 50–80% survival of mice after intraperitoneal doses close to $\frac{1}{2}LD_{50}$, when animals in a control group are completely destroyed. These are aryl derivatives (R' = R'' = H; R = Ar) containing a phenyl, a *p*-chloro-, *p*-hydroxy-, or *p*-methoxy-phenyl, or a *p*-tolyl substituent at the 2 position in the ring.



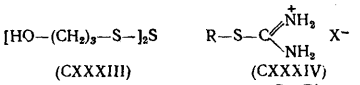
(CXXIX)

(CXXX)
A=CH_2CH_2, CH_2CO, COCH(Me)

Several disulphides and their derivatives have been prepared, and their protective activity has been studied. The absence of biological data prevents assessment of the prospects for unsymmetrical aryl disulphides (CXXIX)[102], disulphides of type (CXXX)[103], or disulphides of the pyrimidine series[104] as protective agents.

$[NaSO_2-(CH_2)_4-S-]_2$ (CXXXI) $[NaSO_2-(CH_2)_4-S-]_2S$ (CXXXII)

High protective activity in experiments on mice was shown by the symmetrical disulphide (CXXXI), which is a derivative of butanesulphinic acid[29]. An intraperitoneal dose of 200 mg kg^{-1} (LD_{50} = 800 mg kg^{-1}) protects 73% of mice that have been irradiated with the absolutely lethal dosage ($I_{ip} \simeq 7$). The corresponding trisulphide (CXXXII) was a still more efficient protective agent[29]. While possessing low toxicity (both intraperitoneal and oral LD_{50} = 900 mg kg^{-1}), this compound at an intraperitoneal dose of 38 mg kg^{-1} is claimed to protect 78% of mice when a control group undergoes absolute destruction ($I_{ip} > 41$), and an oral dose of 300 mg kg^{-1} ensures complete survival of the animals ($I_{or} \simeq 6$). Bis-3-hydroxypropyl trisulphide (CXXXIII) has shown[105] a slight protective effect in experiments on mice.



(CXXXIII) (CXXXIV)
a—R=Et

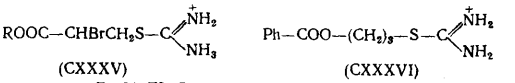
Several papers have appeared on the search for protective agents among alkylthiouronium derivatives, analogues of ethylthiouronium (Etiron, CXXXIV), which exerts a quite pronounced effect. According to Zherebchenko and his coworkers[106] the size of the alkyl group in compounds of this type has a significant influence on the protective activity (Table 10), whereas the nature of the anion plays no special part. It was suggested that Etiron differs from amino-thiols in the mechanism of its protective action. Mukhin et al.[107] supposed that tissue hypoxia underlay the mechanism of protection by Etiron. They report that, in experiments both on mice and on rats, this compound considerably surpasses *S*-2'-aminoethylthiouronium in efficiency.

Table 10. Effect of size of alkyl group in compounds (CXXXIV) on their protective properties[106].

CXXXIV R	Survival of mice, %
Me	40.0
Et	49.0
n-Pr	37.6
n-C_9H_{19}	2.8
Control	1.8

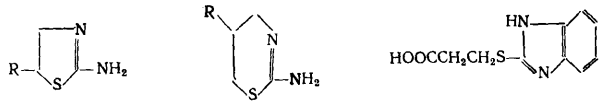
In order to examine the effect of the structure of the *S*-alkyl substituent and of the anion Mizrakh et al.[108] studied several phosphorus-containing alkylthiouronium derivatives both at a cellular level and in experiments on mice with prolonged irradiation (dosage rate 5.8 rad min^{-1}). All the compounds were significantly superior in protective activity to Etiron, which hardly protected the animals at all under these conditions; it was thought that this might be due to the duration of irradiation. The most active compounds were *S*-n-butylthiouronium n-butyl

hydrogen phosphite (CXXXIV: R = C_4H_9 and X = $C_4H_9OPHO_2$) and *S*-ethylthiouronium diethyl orthophosphate (CXXXIV: R = C_2H_5 and X = $(C_2H_5O)_2PO_2$), which ensured the protection of 70–80% of mice and acted against radiation at the chromosomal and cellular level[108].



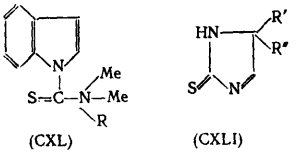
(CXXXV) R=H, Et, C_6H_{13} (CXXXVI)

Slight activity was shown by thiouronium derivatives of α-bromopropionic acid and its esters (CXXXV)[82,109] and also by 3′-benzoyloxypropylthiouronium (CXXXVI)[109]. 2-Acyloxypropyl and other derivatives of thiouronium were inactive.



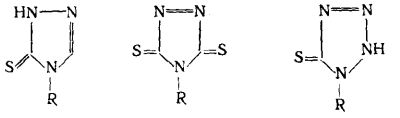
(CXXXVII) R=H, Me, CH_2OH, Br (CXXXVIII) R=H, Cl, Br (CXXXIX)

The protective action of several cyclic analogues of thiouronium of the types (CXXXVII) and (CXXXVIII)[82,110] and (CXXXIX)[79] has been studied. The most interesting results were obtained with 2-aminothiazoline (CXXXVII: R = H)[110]—a possible conversion product of aminothiouronium in the organism—and also for certain of its 5-substituted derivatives, which approach aminoethylthiouronium in efficiency on prophylactic intraperitoneal administration.



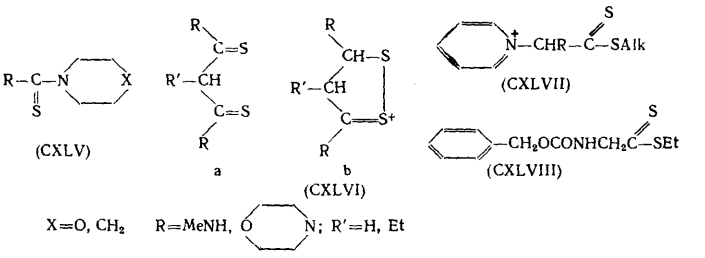
(CXL) (CXLI)

Thiourea derivatives containing a quaternary nitrogen atom (CXL), which are similar in structure to thiouronium compounds, were prepared by Tulecki et al.[111] to study their action against radiation. Here we can also mention cyclic analogues of thiourea—derivatives of imidazole (CXLI)[49,112], triazole (CXLII) and (CXLIII), and tetrazole (CXLIV)[113]—which are able to exist in the tautomeric thiol form. The most efficient were the *p*-halogenoaryltetrazolethiones (CXLIV: R = *p*-HalC_6H_4).



(CXLII) (CXLIII) R=Ar (CXLIV)

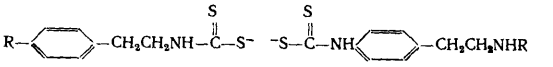
Several other compounds containing a thiocarbonyl group were studied in the search for protective agents. Bitoun et al.[114] studied the action against radiation of several morpholino- and piperidino-thioamides (CXLV), and found that only a few of them had a slight protective effect. Similar results were obtained for a series of dithioamides (CXLVIa). Cyclic analogues of the latter—1,2-dithiolium derivatives (CXLVIb)—only slightly surpass in activity (survival of mice at most 30–40%) the initial thioamides[115].



(CXLV) a b (CXLVI) (CXLVII) (CXLVIII)

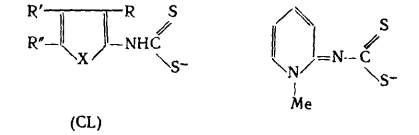
X=O, CH_2 R=MeNH, O N; R′=H, Et

Great attention has been paid during recent years to the search for protective agents among dithiocarboxylic acid derivatives. This line of attack was developed especially intensely by Foye and his coworkers, who showed that substituted derivatives of pyridinodithioacetic acid (CXLVII)[116] and the analogue (CXLVIII)[93] were moderately active in experiments on mice.

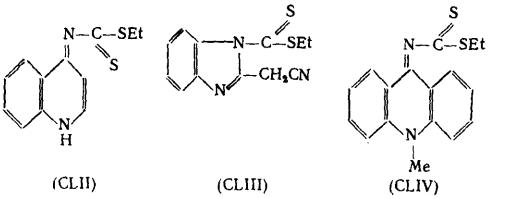


a (CXLIX) b

Several dithiocarbamates have been prepared and studied. No protective activity was detected in two types of derivatives of dithiocarbamic acid based on phenylethylamine (CXLIXa, b)[117], as well as in furan and thiophen derivatives (CL)[118]. It was shown for 1′-methylpyrid-2′-yldithiocarbamic acid (CLI)[119] that dithiocarbamates of the stronger bases have a more pronounced protective effect, though the percentage survival of mice when this compound is used as the 2-amino-1-methylpyridinium salt is not high. Dithiocarbamates of the corresponding 4-imino- and 2-imino-1-methyl-pyrimidines exhibit no protective activity. Among dithiocarbamic esters of 4-amino-2-methylquinoline (CLII), benzimidazole (CLIII), and 9-amino-10-methylacridine (CLIV) only the last showed action against radiation[120].

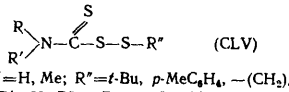


(CL) X=O,S; R=CN, COOEt; R′=H, Me, Ph (CLI)



(CLII) (CLIII) (CLIV)

Field and his coworkers found[76,121] that some of the trithiocarbamates studied by them (CLVa, b) possess quite pronounced protective activity when introduced in large doses.



(CLV)

R=R′=H, Me; R″=*t*-Bu, *p*-MeC_6H_4, $-(CH_2)_4SO_3Na$

a R=R′=H, R″=*t*-Bu; b R=R′=Me, R″=*t*-Bu

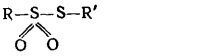
Tulecki et al.[111,122] synthesised several heterocyclic arenesulphinamide derivatives, but gave no data on their protective action.

Studies have continued on the protective action of diammonium phosphoramidothioate[123-125] and its analogues[123], which exhibited little or no activity.



(CLVI) a, R=R'=Me (CLVII)

Compounds containing quadrivalent and sexivalent sulphur have also been studied—as well as bivalent compounds—for use as protective agents. It had earlier been shown[3] that dimethyl sulphoxide (CLVIa) has a protective action against the general irradiation of mice. Arzamastsev et al.[126] studied 40 analogues of this compound (CLVI) and of sulphones (CXVII) with alkyl, ethylenic, vinyl, and acetylenic groups. Only three of these compounds—(CLVI: R = CH_2:CH and R' = CH_2:CH.SO.$[CH_2]_2$), (CLVI: R = R' = t-C_4H_9), and (CLVII: R = CH_3 and R' = CH_2:CH)—had a moderate action against radiation in doses of 33-50% of LD_{50}. Certain thiosulphones (CLVIII) were inactive[64].



(CLVIII)
R=Me, p-MeC_6H_4; R'=Alk, cyclo-C_6H_{11}

A comparative study has been made during recent years of the protective action of the selenium analogues of certain sulphur-containing agents[127-129]. Selenourea protects mice more effectively than does thiourea. The protective action of the selenium analogue of cysteine and certain other selenium compounds is at the same level or even higher, but they are considerably more toxic than the corresponding sulphur compounds.

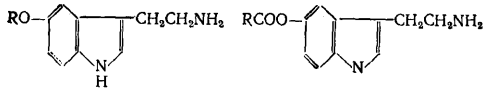
Thus a few highly efficient protective agents, developing activity on intraperitoneal and oral administration in an experiment, have also been discovered among the many (~ 300) sulphur-containing compounds of non-aminothiol structure studied as protective agents against radiation.

IV. HETEROCYCLIC COMPOUNDS

The search for protective agents has been made among nitrogen-containing heterocycles during the past five or six years, as in previous years. Among them derivatives of indole have attracted the greatest attention.

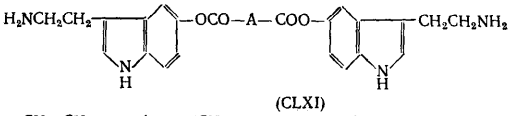
Indolylalkylamines

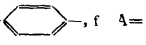
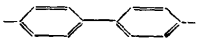
Comprehensive investigations on methods for the synthesis of indolylalkylamines and on their antiradiation properties, made in our country during recent years by Suvorov, Zherebchenko, Semenov, Ermonenko, Shashkov, Antipov, and others[130], led to the production of the protective preparation Mexamine (CLIXa), a close analogue of serotonin (CLIXb), and formed the basis for a further successful search for protective agents in this series of compounds. The study was continued of *N*-peptide derivatives of indolylalkylamines, which showed a marked protective effect (survival of mice 40-60%).[130]



(CLIX) (CLX)
a R=Me (Mexamine)
b R=H (Serotonin)
c R=Et

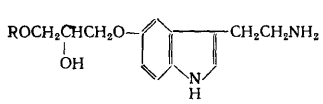
Investigation of the protective properties of a large number of *O*-acyl derivatives of serotonin (CLX)[130-133]—acyl analogues of Mexamine—showed that the introduction of residues of saturated aliphatic acids at the phenolic hydroxyl does not diminish the protective action in comparison with serotonin or Mexamine. Lengthening of the carbon chain in the acyl substituent is accompanied by enhancement of toxicity. Both in the pronounced character of their protective effect and in its duration these compounds are hardly distinguishable from serotonin. Also, like serotonin, they possess little antiradiation activity when taken. *O*-Aroyl and urethane derivatives (CLX: R = CH_3NH, p-ClC_6H_4NH) have a weaker protective effect.



(CLXI)
a A = —CH=CH—, b A = $-(CH_2)_2-$, c A = $-(CH_2)_4-$, d A = $-(CH_2)_8-$
e A = , f A = 

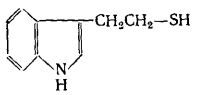
Several other derivatives of serotonin have been prepared and studied in order to find among indolylalkylamines protective agents of prolonged action and active on oral administration. Interesting results have been obtained for diesters (CLXI) formed by dicarboxylic acids—fumaric, adipic, sebacic, terephthalic, and biphenyl-*pp'*-dicarboxylic—with serotonin[132]. These compounds also are the equal of serotonin and Mexamine in protective activity. Their toxicity is on the average several times higher than that of the latter. When introduced into mice at different times before irradiation, they exhibited more prolonged action against radiation than did serotonin or Mexamine. Data for several of these compounds show (Table 11) that the most efficient as a protective agent is that derived from succinic acid (CLXIb), with I_{ip} = 20. Compounds (CLXId, e) retain their high protective properties for 1 h, in contrast to Mexamine and serotonin. When taken orally the bis-*O*-acyl derivatives, like the monoacyl compounds, exert a slight protective effect.

Addition of a glycerol molecule to tryptamine at position 5 of the indole ring (CLXIIa)[132] enhances the effectiveness of tryptamine against radiation. Prophylactic application of this compound gives 60% survival of mice with 92% mortality of animals in a control group. Replacement of the γ-hydroxyl by an alkoxy-group (CLXIIb) does not enhance the antiradiation properties, and introduction of a hydroxyethyl group (CLXIII) leads to a loss of activity. The *O*-glucoside of serotonin and derivatives of 3-dialkylamino-3-deoxy-analogues of 1-indol-3'-ylglycerol were ineffective[133].

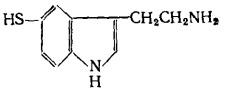


(CLXII) a R=H, b R=Alk
(CLXIII) R=HO—$(CH_2)_2$—

Comparing protective activities in experiments under the same conditions, Deanovič showed[134] that serotonin somewhat surpasses Mexamine, and 5-ethoxytryptamine (CLIXc) is inferior to both. He even[135] discovered that the thiol analogue of tryptophol (CLXIV) and the corresponding disulphide exerted no strong action against radiation, whereas 5-mercaptotryptamine (CLXV) protected mice only slightly more weakly than did serotonin, even with a superlethal dose of radiation.



(CLXIV)

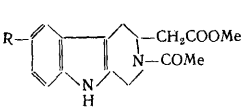


(CLXV)

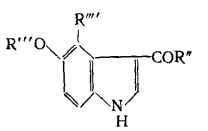
Table 11. Protective properties of serotonin, Mexamine, and their analogues (CLXI)[132].

CLXI A	Doses, mmole kg^{-1}		Time to irradiation, h	Survival, %	I_{ip}
	LD_{50}	ED			
a	0.288	0.070	0.1	60.0±10.9	6.6
			1.0	27.6±8.3	
			2.0	20.0±12.6	
b	0.800	0.070	0.1	75.0±9.7	20.0
			1.0	35.0±10.7	
			2.0	10.9±9.5	
c	0.324	0.070	0.1	60.0±10.9	8.5
			1.0	36.6±8.8	
			2.0	0	
d	0.107	0.070	0.1	67.8±8.9	2.6
			1.0	55.1±9.4	
			2.0	20.0±12.6	
e	0.084	0.070	0.1	94.7±9.15	2.3
			1.0	51.8±9.6	
			2.0	10.0±9.5	
Mexamine	1.04	0.30	0.1	53.8±9.8	18.6
		0.10	0.1	78.5±13.3	
		0.30	0.3	33.3±12.2	
		0.10	0.3	0	
Serotonin		0.04	0.1	64.0±11.3	
		0.150	0.3	0	
		0.40	0.3	6.7±6.5	

From tryptophol Japanese workers[136] prepared several compounds of tryptamine structure, including tricyclic compounds, e.g. (CLXVI), but they did not report results of their biological tests.



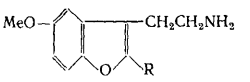
(CLXVI)



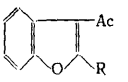
(CLXVII)

Among the many (~ 100) indole compounds studied of type (CLXVII), containing a 3-carbonyl group, Shadurskii and Maksimenko[137] were unable to find any which would protect irradiated mice by more than 20–30%. These workers and also Il'yuchenko et al.[138] studied the protective activity of several types of benzofuran compounds (CLXVIII–CLXX), which are isosteric with indole compounds and include an analogue (CLXVIII) of Mexamine.

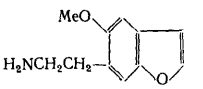
Most active among them (40% protection) was the aminoethyl derivative (CLXX)[138].



(CLXVIII)

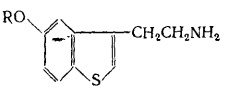


(CLXIX)

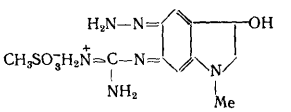


(CLXX)

According to Deanovič[135] the benzothiophen analogue (CLXXIa) of Mexamine has no action against radiation at all, whereas the isostere (CLXXIb) of serotonin is closely similar in efficiency to the latter, becoming inferior only at superlethal radiation doses[135,136].



(CLXXI a R=Me, b R=H)

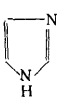


(CLXXII)

Japanese workers[139,140] made a detailed study of the protective properties of 5-hydrazonoadrenochrome-6-guanidinium methanesulphonate (CLXXII), which is a modification of an indoline metabolite. This relatively non-toxic compound (subcutaneous LD_{50} = 1834 mg kg^{-1}) shows a pronounced action against radiation in small doses of ~ 5 mg kg^{-1}. Under the name "S-adchnon" this protective agent, which acts on haemapoietic organs, has been proposed for clinical application to diminish the harmful effect of irradiation during the X-radiotherapy of human beings.

Other Nitrogen-containing Heterocycles

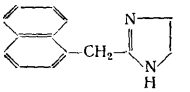
Investigation of the protective activity of imidazole (CLXXIII) and its derivatives has continued during recent years[141–143]. An intraperitoneal dose of imidazole itself of 350 mg kg^{-1} introduced 5 min before irradiation protects ~ 80% of mice; introduction 4½ h before and 1 min after irradiation halves the protective effect. Benzimidazole (CLXXIV) and 2-naphth-1'-ylmethylimidazoline (CLXXV)—the latter is the well known medicinal Naphthisin—are just as active[143].



(CLXXIII)

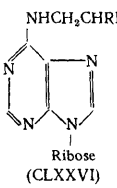


(CLXXIV)

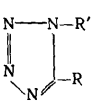


(CLXXV)

It has been reported that diphenylhydantoin improves the radiation resistance of mice[144], and that 3-hydroxypyridine derivatives have high protective activity[145].



(CLXXVI)



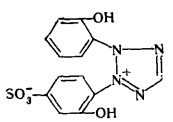
(CLXXVII)

a R=H, R'=ClC$_6$H$_4$;

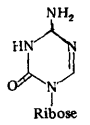
b R=NHNH$_2$, R'=Ph

Interesting results were obtained for the protective action of 6-substituted adenine ribosides (CLXXVI)[146]. In small doses compounds of this type with various substituents in the ethylamino-chain (R = H, CH_3; R' = CH_3, OH, NH_2, SH, CH_2NH_2, CH_2OH) show a well defined effect against radiation. Ribosides of 6-hydrazino- and 6-methylthio-purines were inactive, as were analogues

(CLXXVI) having the ethylamino-chain at position 8 in the ring system.



(CLXXVIII)



(CLXXIX)

Action against radiation has been observed also among tetrazoles. The most active were 1-chlorophenyl derivatives (CLXXVIIa), as well as 5-hydrazino-1-phenyltetrazole (CLXXVIIb)[152] and 2-*o*-hydroxyphenyl-3-2′-hydroxy-4′-sulphophenyltetrazole (CLXXVIII).

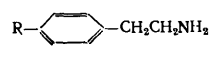
Czech workers[147] showed that certain aza-derivatives of pyrimidine have a protective effect in small doses. The highest survival rate of mice (55%) was observed with 5-azacytidine (CLXXIX) introduced 24 h before irradiation. The protective action was attributed[147] to a favourable effect on the proliferation of the stem cells responsible for repopulating bone marrow.

Protective action has been reported for thiamine[148], which contains pyrimidine and thiazole rings, derivatives of tetrahydropteridine[149], and haematoporphyrin[150].

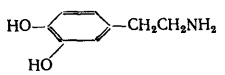
V. COMPOUNDS OF DIVERSE STRUCTURE

Amino-compounds

Protective action has been reported[151] in propylenediamine and in 2-methylpropylenediamine. *p*-Alkoxyphenylethylamines (CLXXX) exhibit activity against radiation[152], which diminishes with increase in the length of the hydrocarbon chain from C_4 onwards. The most active was *O*-methyltyramine (CLXXXa), which in an intraperitoneal dose of 50 mg kg^{-1} gave survival rates of 47–75% of irradiated mice (dosage rate 400–600 rad min^{-1}). Oral administration of this compound protects up to 40% of animals. The protective activity disappears when one or two amino-hydrogen atoms are replaced by alkyl or acyl. Il'yuchenko et al.[153] found that *O*-methyltyramine has the average action against radiation when mice are irradiated at rates of 2400, 216, and 65 rad min^{-1}, and they investigated the prophylactic protective activity of tyramine and its *O*-alkyl derivatives when mice were exposed to 10 rad min^{-1}. Under these conditions the *O*-pentyl and *O*-dodecyl derivatives (CLXXX: R = $C_5H_{11}O$, $C_{12}H_{25}O$) were more effective.

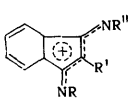


(CLXXX) a R=MeO

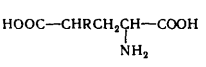


(CLXXXI)

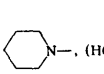
Detailed investigation of the prophylactic protective action of dopamine (CLXXXI) showed[154] that a dose of 100 mg kg^{-1} protects ~ 60% of irradiated mice.



(CLXXXII)

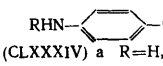


(CLXXXIII)

R = F, Et_2NCH_2–, , $(HOCH_2CH_2)_2N$–

Salts of 1-amino-3-iminoind-2-enes (CLXXXII) diminish the genetic damage in *Drosophila* caused by irradiation[155].

Protective activity was observed in certain γ-substituted glutamic acids (CLXXXIII)[84].



(CLXXXIV) a R=H, b R=OH

The study of analogues of *p*-aminopropiophenone (CLXXXIVa) has continued during recent years. *p*-Hydroxyaminopropiophenone (CLXXXIVb), a possible metabolite of (a), possesses approximately the same protective effect[156]. Vladimirov et al.[157] studied several aminopropiophenone and aminobenzophenone derivatives (Table 12), and showed that the action of most of them against radiation was directly dependent on their ability to form methaemoglobin, which requires the presence of a free amino-group in the molecule. These compounds include substances with a moderate protective action without causing the development of methaemoglobinaemia in the animals. Table 12 lists some of the most active compounds of this type.

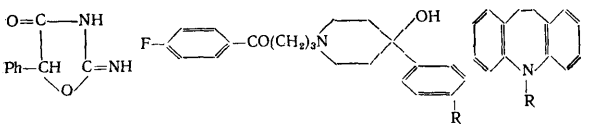
Table 12. Protective properties of aminopropiophenones[157].

Compound	Dose, mmole kg^{-1}	Survival, %
CLXXXIV a	0.2	60
CLXXXIV b	0.2	65
p-$H_2N-C_6H_4C(=NOH)Et$	0.25	60
o-$H_2N-C_6H_4COEt$	1.5	45
p-$H_2N-C_6H_4COEt$	0.5	75

Intraperitoneal introduction of phenylhydrazine 5–8 days before irradiation of mice resulted in a high survival rate[158].

Psychotropic Agents

These agents include compounds of diverse chemical structure exerting a prophylactic effect against radiation and those which are psychotropic medicinals. Slight protection is shown by the magnesium complex of Azoxodone (CLXXXV), a stimulant of the central nervous system[159]. The activity drops sharply in the absence of magnesium. Uray and his coworkers[160,161] studied the protective activity against radiation of tranquilisers of the Haloperidol series (CLXXXVIa). Intravenous injection of one of these preparations—Movotren (CLXXXVIb), which contains *p*-tolyl instead of a *p*-chlorophenyl substituent—into mice after 30 and 60 min protects up to 60–70% of the animals. The same workers[162] discovered that antidepressants—Imipramine and Trimipramine (CLXXXVIIa, b)—are able to increase the survival rate of irradiated mice.



(CLXXXV)

(CLXXXVI) a R=Cl, b–R=Me

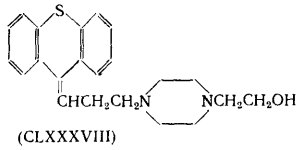
(CLXXXVII) a R=$-CH_2CH_2CH_2N(Me)_2$ b R=$-CH_2CH(Me)CH_2N(Me)_2$

According to Locker et al.[163,164] certain thymoleptics of phenothiazine and thioxanthen structure develop a marked

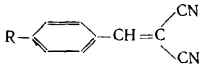
protective effect against radiation, which is strongest with Sordinol (CLXXXVIII). The effectiveness of this preparation was found to increase up to a certain limit with increase in the time between administration and irradiation.

Various Compounds

Among the > 40 nitriles and isothiocyanates studied, only the malononitrile derivative (CLXXXIX) exhibited a weak protective action in experiments on mice[165]. Activity against radiation was shown by diphenylmethanol derivatives with dimethyl- and diethyl-amino-groups in one and two benzene rings[166] and by 1-hydroxy-2-dimethylallylmethylamino-4-butylphenol[167]. *cis*-Dichlorodiammineplatinum develops a protective action in small doses: introduction into mice 1 and 24 h before irradiation produced a survival of 70%.[168]



(CLXXXVIII)



(CLXXXIX)
R=H, OH, Cl

Summarising, we may conclude that a vigorous search for protective agents against radiation has been made during the past 5–6 years among compounds of diverse structure. Most of the almost 1500 substances studied were sulphur-containing compounds, predominantly of amino-thiol structure. Considerable progress has been made during these investigations, the most important advances being listed below.

1. Compounds of high activity against radiation under the experimental conditions and possessing great therapeutic latitude have been prepared.
2. Highly efficient protective agents for oral administration have been found under the experimental conditions.
3. Comprehensive information has accumulated on the influence of the chemical structure of various classes of compound on their protective activity.

The main result must be to confirm and to provide a firmer basis for the possibility and promise of chemical protection of the living organism from ionising radiation.

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