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New Chemical Agents for Protection against Ionising Radiation

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Data obtained in the search for radioprotectants among organic monomeric compounds during the period from 1974 to 1983 are surveyed.
The bibliography includes 332 references.

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I. INTRODUCTION

Despite the extremely modest advances achieved as a result of many years of studies undertaken to find new chemical means for protection against ionising radiation, the interest in this problem has not weakened. Interesting monographs[1,2] and reviews,[3-7] devoted to the search for, synthesis, and applications of chemical radioprotectants, have been published in recent years but they cover data obtained over a long period or deal with only individual aspects of this question. Since the need for the search for chemical prophylactic radioprotective agents has increased every year, it is of interest to follow the development and characteristics of the research in this field during recent years.

A review published in 1975[8] summarised the results of the search for chemical radioprotectants during the period between 1968 and 1973. This review surveys and gives a systematic account of the literature data obtained in the search for prophylactic antiradiation agents among new organic monomeric compounds published during the last ten years (from 1974 to 1983 inclusive).

So far as possible, the entire data have been arranged systematically in a manner analogous to that employed in an earlier review.[8]

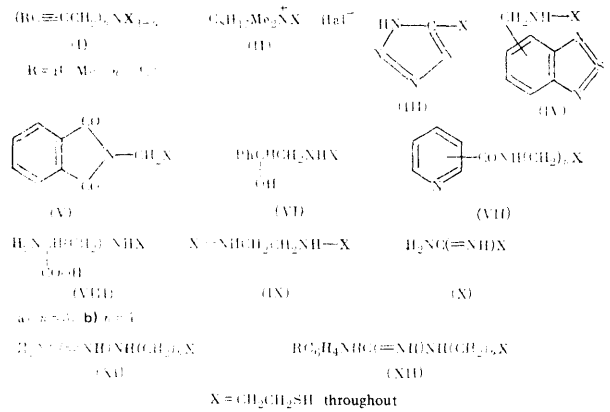
II. SULPHUR-CONTAINING COMPOUNDS—DERIVATIVES OF β-MERCAPTOETHYLAMINE

Recently, new structural analogues and various derivatives of one of the oldest and most widely known radioprotectant—β-mercaptoethylamine (MEA) have appeared. The simple fragment $\rangle N-\overset{|}{C}-\overset{|}{C}-S-$ constitutes the basis of the *N*- and *S*-substituted derivatives synthesised: thiols, disulphides, thiosulphates, phosphorothioates, isothiuronium salts, thiazolidines, etc. The available data will be considered in this sequence.

1. Aminoalkanethiols

The syntheses of a series of MEA derivatives with an unsubstituted thiol group containing various substituents at the nitrogen atom have been described. It has been observed that, among compounds with unsaturated hydrocarbon groups, the alkyl derivatives, for example compound (I), have proved to be the most active and least toxic.[9] It has been shown that the radioprotective effect (RPE) is reduced on quaternisation of the amino-group as in compound (II)[10] and after the introduction of heterocyclic residues—the tetrazolyl [compound (III)[11]], benzo-2,1,3-thiadiazolylmethyl [compound (IV)[12]], phthalimide [compound (V)[13,14]], and 2-hydroxy-2-phenylethyl [compound (VI)[15]] residues.

N-Pyridinoyl derivatives (VII) have been proposed as radioprotectants.[15]



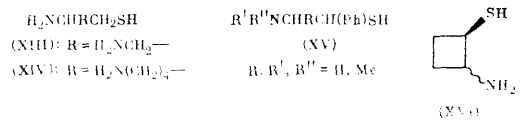
X = CH_2CH_2SH throughout

The MEA derivatives obtained as a result of multistage synthesis, namely the ornithine derivative (VIIIa) and the lysine derivative (VIIIb), have different protecting effects on irradiated mice:[16] compound (VIIIa) administered intraabdominally (i/a) in a dose of 150–300 mg kg^{-1} ensures a 50–100% survival rate, whilst compound (VIIIb) is inactive. Neither compound is effective when administered perorally (p/o).

Compound (IX),[17] which exhibits an antioxidant activity, has been proposed as a radioprotectant.

The replacement of the amino-group in MEA by the amidine group as in compound (X) leads to an appreciable increase of the radioprotective effect and to a decrease of toxicity.[18] In order to investigate antiradiation properties, a series of mercaptoalkylguanidines have been synthesised—unsubstituted [compound (XI)[13]] and aryl-substituted [compound (XII)[19]]. Among them, compounds (XI, $n = 0$) and (XII, R = H, $n = 1$) proved to be the most active.

MEA analogues with various substituents in the hydrocarbon chain have been described. The introduction of the aminomethyl residue at the carbon atom nearest to the nitrogen atom in MEA [compound (XIII)] entails a sharp decrease of activity, while the aminobutyl analogue (XIV) is highly effective in small doses administered intra-abdominally and perorally, although its toxicity is much higher.[20]



It has been shown in experiments on mice[21] that in the series of *C*-phenyl-substituted MEA derivatives (XV), substitution of the hydrogen atoms at the C and N atoms by methyl groups results in a decrease of the radioprotective activity. The introduction of the mercaptomethyl group at one of the carbon atoms in the MEA molecule does not enhance the protecting effect.[22]

The relation between the RPE and structure has been investigated[23] for a series of cyclic MEA analogues—derivatives of *cis*- and *trans*-2-amino-1-mercaptocyclobutane (XVI) and their analogues. The greatest RPE was exhibited by the *cis*-isomers of compound (XVI) when they were administered intra-abdominally or enterally. Analogous cyclopropyl derivatives have also been studied.[24] A series of MEA derivatives having substituents at the sulphur atoms have been synthesised and it has been shown that the introduction of an unsaturated substituent, as in compound (XVII), results in the disappearance of the protecting effect.[9] Compounds having an amidinoethyl substituent, as in compound (XVIII), exhibit a moderate RPE.[25] It is of interest that the introduction of an acetyl substituent into compound (II) to give compound (XIX) decreases the toxicity but the radioprotective properties are preserved.[10]

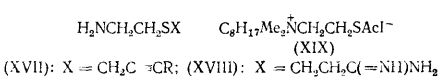


Table 1. Comparative effectiveness of MEA and compound (XIV).[24]

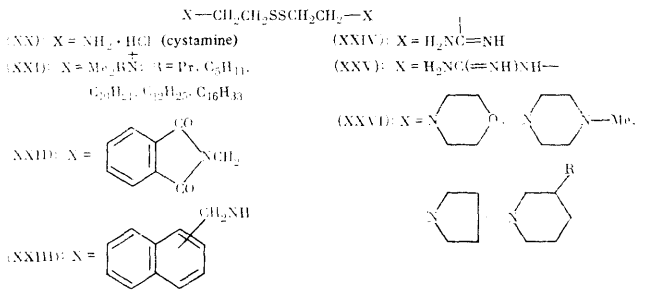
$H_2NCHRCH_2SH$		LD_{50}, mg kg^{-1}	ED, mg kg^{-1}	% protection	*I*
MEA.HCl	i/p	250	150	87	3.1
(R = H)	p/o	615	300	73	3.6
(XIV).2HCl	i/p	88	25	90	6.5
[R = $H_2N(CH_2)_4$]	p/o	450	75	70	10

Notation. LD_{50} is the dose of the test substance which results in the death of 50% of animals and ED is the effective dose. *I* = protectant index.

The number of closest MEA analogues (mercaptoalkylamines) investigated in recent years is small—approximately 50 (during the previous period 1968–1970, about 130 of these were described); among these compounds, one merits attention, namely 2,6-diaminohexane-1-thiol (XIV). Its advantage over MEA is clearly seen from the data in Table 1.

2. Aminoalkyl Disulphides

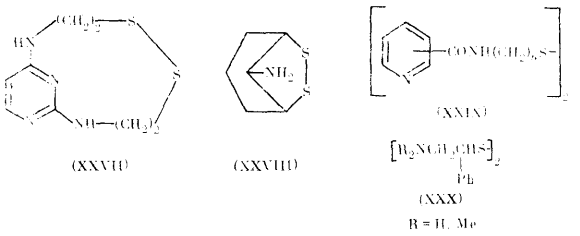
The interest in the search for more effective cystamine (XX) analogues has not weakened. It has been confirmed[10] that the replacement of the free amino-groups in the molecule of compound (XX) by quaternary ammonium groups, including those incorporating higher alkyl groups, as in compound (XXI), results in a decrease of the RPE. The same result has been obtained[13] when the amino-groups were substituted by phthalimidomethyl residues (XXII). The 1- and 2-naphthylmethyl derivatives of cystamine (XXIII) proved to be inactive:[12]



The bisamidine analogue (XXIV)[18] and the bisguanidine analogue (XXV)[13] of cystamine are not inferior to the latter as regards activity.

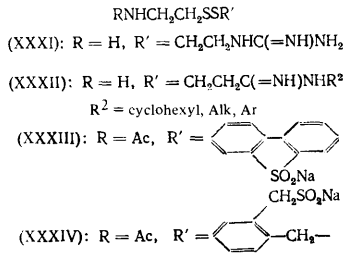
A pronounced radioprotective activity has not been observed in a whole series of bis(aminoethyl) disulphides containing at the nitrogen atoms heterocyclic substituents such as the 2-quinoxalinyl,[27] benzo-2,1,3-thiadiazol-4-ylmethyl and the corresponding 5-methyl,[12] 2-pyridylmethyl,[27] 2-pyrimidinyl,[27,28] and phenyltetrazolyl[27] groups. On the other hand, it has been observed that compounds of the type of (XXVI) with the morpholine and 4-methylpiperazine groups exhibit an RPE which is not inferior to that of unsubstituted cystamine.[27,28]

The macrobicyclic disulphide (XXVII),[29] the bicyclic disulphide (XXVIII),[30] and the disulphides containing pyridinecarboxylic acid residues (XXIX)[15] have been described as radioprotective agents.



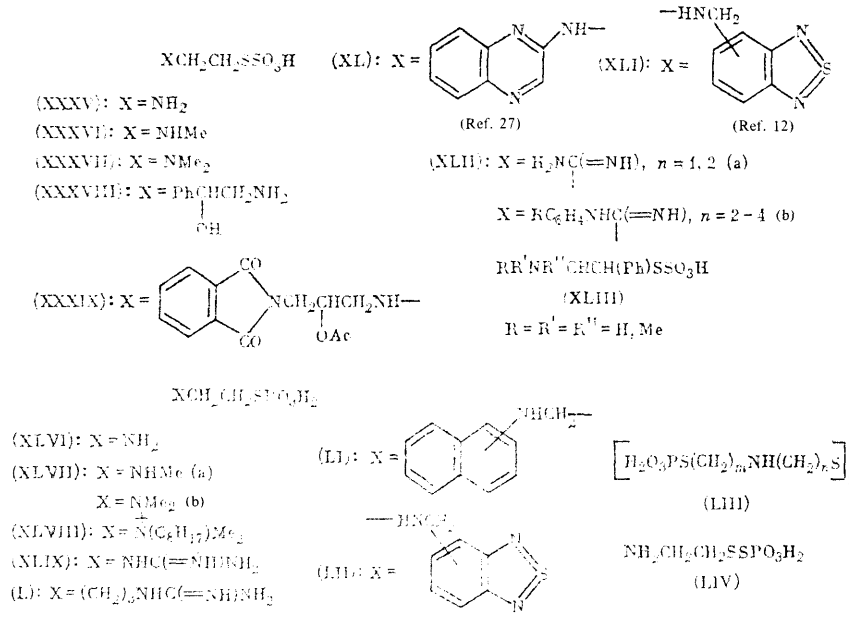
A fairly distinct antiradiation effect has been exhibited by certain *C*-phenyl-substituted cystamines (XXX).[21,31]

Interesting results have been obtained in a study of the asymmetric disulphides (XXXI),[13] (XXXII),[32,33] (XXXIII), and (XXIV),[34] containing the aminoethyl fragment. Thus the last compound is superior in its activity to the disulphide (XX) and all the analogues quoted above; its LD_{50} (for i/a and p/o administration) is greater than 900 mg kg^{-1} and ensures 100% protection of mice against the absolutely lethal radiation dose when administered intra-peritoneally in a dose of 75 mg kg^{-1}; when taken orally the dose is 600 mg kg^{-1}



3. Aminoalkyl Thiosulphates

Much less attention than in previous years has been devoted to derivatives of *S*-aminoethylthiosulphuric acid (XXXV) (Bunte salts). It has been found that methylation of the nitrogen atom, as in compounds (XXXVI) and (XXXVII), results in an appreciable enhancement of the protecting activity:[35,36]



As for other MEA derivatives, the introduction of the naphthylmethyl residue at the nitrogen atom eliminates the protecting effect almost completely.[12] Compounds (XXXVIII) and (XXXIX) also showed a low activity.[14] Like the disulphides, the majority of Bunte salts with heterocyclic substituents at the nitrogen atom proved to be inactive and only compounds (XL) and (XLI) led to 60–70% survival rate of mice and only after administration in near-toxic doses.

The amidine [compound (XLIIa)[18]] and arylguanidine [compounds (XLIIb)[19]] derivatives have been investigated. Compound (XLIIa, $n = 2$) is somewhat superior to compound (XXXV) as regards activity.

C-Phenyl derivatives (XLIII) showed a pronounced protecting effect.[21,31]

It is noteworthy that a much greater number of compounds with a similar structure were investigated in the previous period and among them highly effective radioprotectors were discovered.[8]

4. Aminoalkyl Phosphorothioates

The main trend in studies in this field involves the discovery of radioprotectants most promising for practical use in cancer X-radiotherapy and not the synthesis of new compounds.[37–39] Among a series of other compounds, *S*-[*N*-(3-aminopropyl)-2-aminoethyl]phosphorothioic acid (gammaphos, WR-2721), which is at present undergoing clinical tests in the USA and Japan, has attracted special attention.[40,41]

Several studies have been devoted to the synthesis and investigation of the RPE of derivatives of polyaminopolyalkyl phosphorothioates widely represented in the previous period. It has been shown that the introduction of the hydroxy-group into the hydrocarbon chain (see Table 2) does not as a rule reduce the RPE after intra-peritoneal administration to mice, but these substances do not protect when administered orally.[14,37,39]

Table 2. The radioprotective activity of $RSPO_3H_2$ administered intra-peritoneally to mice.[14]

R	LD_{50}, mg kg^{-1}	ED, mg kg^{-1}	% protection
$H_2N(CH_2)_3NHCH_2CH(OH)CH_2$—	875	200	100
$H_2NCH_2CH(OH)CH_2NH(CH_2)_2$—	825	300	93
$H_2NCH_2CH(OCOMe)CH_2N(CH_2)_2$—	>1250	500	100
$H_2NCH_2CH(OH)CH_2NH(CH_2)_3$—	>700	600	100
$HO(CH_2)_2NH(CH_2)_2NH(CH_2)_2$—	200	100	60
$H_2NC(CH_2OH)_2CH_2$—	>1250	250	100
$H_2N(CH_2)_2NH(CH_2)_2$— (XLIV)	1020	300	100

The introduction of an additional aminoalkyl group increases the toxicity and decreases somewhat the RPE of compounds (XLV) compared with compounds (XLIV); the greatest dose reduction factor (DRF), amounting to 1.8, is

shown by compounds with $l = m = n = 2$ and $l = n = 2$, $m = 3$.[42]

$H_2NCH_2CH_2CH_2NHCH_2CH_2SPO_3H_2$
(XLIV)
$H_2N(CH_2)_l NH\,(CH_2)_m\,NH(CH_2)_nSPO_3H_2$
(XLV)

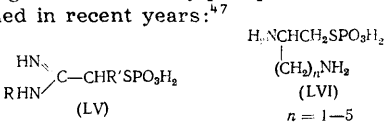
It has been found that the replacement of the hydrogen atoms by the methyl group, as in compound (XLVIIa), at the nitrogen atom of aminoethylphosphorothioic acid (XLVI) does not decrease the RPE; the presence of two methyl groups results in the loss of radioprotective properties by compound (XLVIIb),[35] but the introduction of an additional octyl substituent, as in compound (XLVIII), enhances the RPE with a slight increase of toxicity.[10]

It has been reported[43] that the guanidine derivatives (XLIX) and (L) exhibit a radioprotective activity. As for the aminoalkanethiols and disulphides, the naphthylmethyl derivatives (XLI) proved to be inactive.[12] *N*-Benzo-2,1,3-thiadiazolylmethylaminoethylphosphorothioic acids (XLII) showed the highest RPE.[12]

It was found[44] that the nature of the cation linked to compound (XLVI) has different effects on the toxicity and radioprotective activity; the piperidine and morpholine salts proved to be comparable to sodium salts in terms of their specific activity, while adamantylammonium salts proved to be inactive.

It has been shown recently[45] that derivatives of aminoethylphosphorothioic acid, containing the alkyl disulphide group at the nitrogen atom, as in compound (LIII), exhibit radioprotective activity in doses of 12.5–200 mg kg^{-1}. A new type of phosphorothioic acid derivatives has been discovered and investigated by Sverdlov and co-workers,[46] who showed that the disulphide (LIV) protects up to 55% of mice against radiation over a period of 15–60 min when introduced intra-peritoneally. An approximately the same effect has been obtained also in the case of gamma-neutron irradiation. The substance is inactive when introduced enterally.

Studies designed to search for radioprotectants among amidine analogues of aminoethylphosphorothioic acid (LV) have continued in recent years:[47]


(LV)

(LVI)
$n = 1$—5

R = H, R′ = Alk
R′ = H, R = 1-adamantyl (Ad),
3-Me=Ad, 3, 5, 7-Me_3=Ad

It has been shown that the replacement of the hydrogen atom at the carbon atom by the methyl group, as in compound (LV, R′ = Me), hardly affects the toxicity of the protecting effect when introduced intra-peritoneally but in the enteral administration the toxicity is reduced by a factor of ~1.5, while the effective protective dose increases by approximately the same factor. With increase of the bulk of the group R′, the toxicity of the compounds increased with a simultaneous reduction and even loss of radioprotective activity. Unexpectedly, it was found that the introduction of methyl groups into the adamantyl group results in only a sharp increase of toxicity in the complete absence of a protecting effect (possibly owing to the sharp reduction of solubility in water).

The antiradiation activity of *C*-aminoalkyl derivatives (LVI) has been investigated[20] and it has been shown that they are not inferior in this respect to compound (XLVI) when introduced intra-peritoneally, but, with the exception of compound (LVI, $n = 4$), they are all inactive when introduced enterally. It is of interest that the *L*-isomers of compounds (LVI, $n = 3$ or 4) showed no differences as regards the RPE compared with the corresponding racemates. Table 3 presents data for compounds of this series.

5. Aminoalkylisothiuronium Salts

A number of studies have been devoted to the synthesis and radioprotective properties of derivatives of 2-aminoethylisothiuronium (AET) (LVII, R = R′ = R″ = H, $n = 0$), including cyclic compounds.

The toxicity and radioprotective activity of various *N*- and *C*-substituted AET (LVII, $n = 0$ or 1) and the corresponding cyclic forms, namely 2-aminothiazolines and 2-aminothiazines (LVIII, $n = 0$ or 1), have been investigated.[48–51] It has been shown that the cyclic forms, which are the products of the metabolism of AET derivatives in the organism, are less active as radioprotectants; all new compounds are inferior to AET in their antiradiation activity but they exhibit a broader spectrum of therapeutic activity and the duration of their RPE is longer.

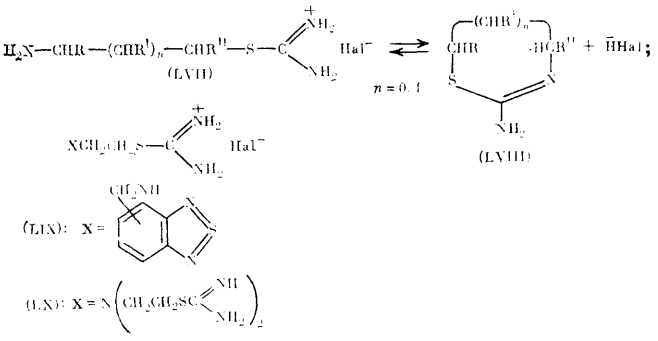

(LVII)
(LVIII)
(LIX): X =
(LX): X = N(CH2CH2SC(NH)NH2)2

Table 3. The radioprotective activity of compound (LVI) in mice.[20]

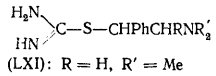
n	Method of administration	LD_{50}, mg kg^{-1}	ED, mg kg^{-1}	% protection	*I*
1	i/p	>900	400	80	>4
2	i/p	>1250	250	100	>10
3	i/p	>1000	250	100	>8
4	i/p	325	62.5	80	9.4
	p/o	750	500	80	2.7
5	i/p	500	200	100	5
	p/o	>1000	400	30	>3
(XLIV)	i/p	1020	300	100	6.8
	p/o	1500	600	100	5

It has been found in relation to *S*-(2-aminopentyl)isothiuronium salts (LVII, R = Pr, R′ = R″ = H, $n = 0$) that[52] both the optical isomers of this compound and the racemic form exhibit a pronounced RPE in experiments on cells but hardly protect irradiated mice. The *N*-benzo-2,1,3-thiadiazolinyl-3-methyl derivative of AET (LIX)[12] as well as the unusual tri-isothiuronium derivative (LX)[53] showed a weak RPE.

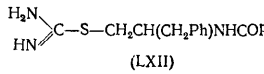
It has been shown[54–56] that the adenosine triphosphate salt of AET (adeturon) exhibits a high radioprotective activity under the conditons of acute irradiation and also in prolonged and fractionated irradiation. In experiments on monkeys 50% protection was achieved after intravenous

administration in a dose of 150 mg kg^{-1} 6–15 min before irradiation.

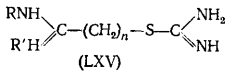
Interesting results have been obtained by modifying the carbon chain of AET with aryl substituents. Compounds (LXI)[21,31] and (LXII)[31] exhibit a high RPE, but the replacement of a hydrogen atom in compound (LXI) by the methyl group, as in compound (LXIII), or the replacement of the dimethylamino-group by the piperidino-group, as in compound (LXIV), fully abolishes the radioprotective properties of the molecule.[21]



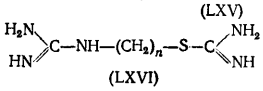
(LXI): R = H, R′ = Me
(LXIII): R = R′ = Me
(LXIV): R = H, R′ = $(CH_2)_5$



(LXII)



(LXV)



(LXVI)

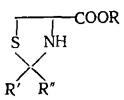
A series of AET derivatives in which the amino-group has been replaced by the amidino-group, as in compound (LXV),[18,57,58] or the guanidino-group, as in compound (LXVI),[19] have been synthesised. The synthesis and the radioprotective activity of compounds in the (LXV) series with different substituents at the nitrogen atom of the amidino-group and also with different lengths of the carbon chain have been studied in detail[57,58] and it has been shown that, when R = R′ = H, compounds with n = 1 or 3 are effective, while those with an even number of methylene groups are completely inactive. Among derivatives (LXV) substituted at both nitrogen atoms, the compound with the 2-methoxyphenyl residues showed the highest activity.[58]

Compounds in which the isothiuronium group is included in a ring will be considered together with other heterocyclic compounds.

6. Thiazolidines

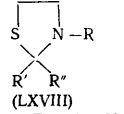
In contrast to other derivatives of mercaptoethylamine, more studies have been devoted to its cyclic analogues, namely thiazolidines, than in the previous period. These compounds have attracted attention because some of them are capable of protecting animals when administered several hours before irradiation,[4,59] showing at the same time a broad spectrum of therapeutic activity.[60]

It has been shown[59,61,62] that, among derivatives of 2,2-dialkylthiazolidine-4-carboxylic acid (LXVII), the methyl esters (LXVII, a and b) are greatly inferior to the corresponding ethyl esters (LXVII, c and d) as regards the RPE. The ester (LXVIId) proved to be an effective radioprotectant; its hydrochloride (LD_{50} = 1750 mg kg^{-1}) ensured 90% protection of mice when administered intra-peritoneally in a dose of 813 mg kg^{-1} 15–30 min before irradiation:[59,61]



(LXVII)

a) R = R″ = Me, R′ = Et; b) R = R′ = R″ = Me; c) R = R′ = Et, R″ = Me; d) R = Et, R′ = R″ = Me; e) R = R″ = Me, R′ = CH_2COOEt; f) R = Et, R′ = COOEt, R″ = Me; g) R = H, R′R″ = $(CH_2)_n$ (n = 5–7); h) R = Et, R′ = H, R″ = CHPhCOOEt



(LXVIII)

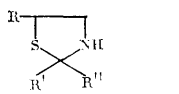
R = H, COOEt; R′ = Me, Pr, Ph
R″ = CH_2COOEt, $CH(CH_2Ph)COOEt$

The introduction of the ethylcarbonylmethyl [compound (LXVIIe)], ethoxycarbonyl [compound (LXVIIf)], or ethoxycarbonylphenylmethyl [compound (LXVIIh)] residues in the 2-position in place of the alkyl group full abolishes activity.[53,61] The absence of protection has been observed[63] also for the products of the condensation of cysteine with cyclic ketones (LXVIIg).

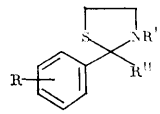
Comparison of the toxicities and radioprotective activities of the alkyl esters of 2,2-dimethylthiazolidine-4-carboxylic acid (LXVIII, R = alkyl, R′ = R″ = Me) and the corresponding cysteine esters showed[62] that the latter are less toxic and their radioprotective activity is higher. The esters of lower alcohols (ethyl and propyl) proved to be less toxic in both series.

A series of compounds containing the ethoxycarbonylmethyl group in the 2-position in the thiazolidine ring [compounds (LXVIII)] have been synthesised and investigated.[64] Among them, compound (LXVIII, R = H, R′ = Pr, R″ = CH_2COOEt) proved to be the most active. After the introduction of the ethoxycarbonyl group at the nitrogen atom, which increases the stability of the heterocycle, a fairly pronounced effect is maintained in the methyl derivative (LXVIII, R = COOEt, R′ = Me, R″ = CH_2COOEt).

Interesting results have been obtained in the study of thiazolidines without carboxy-groups. The high effectiveness of 2,2,5-trimethylthiazolidine (LXIX), whose hydrochloride protects 90% of mice irradiated with an absolutely lethal dose after intra-peritoneal administration in a dose of 500 mg kg^{-1} (LD_{50} = 1150 mg kg^{-1}) during periods from 2 to 60 min before irradiation.[59]



(LXIX): R = R′ = R″ = Me;
(LXX): R = H, R′ = Me, R″ = Et;
(LXXI): R = H, R′ = H, Me, R″ = Alk, alkenyl, alkynyl



(LXXII)
R = H, Hal, OH, Me, MeO;
R′, R″ = H, Me



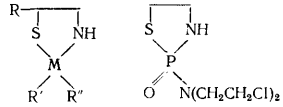
(LXXIII)
R = H, Alk, Ar

Its isomer (LXX) has a somewhat lower activity and is more toxic (LD_{50} = 845 mg kg^{-1} for the hydrochloride).[59] It has been found that the RPE increases with increase of the degree of unsaturation of the substituent R″, as in compound (LXXI).[9]

Among 2-arylthiazolidines (LXXII) (more than 30 compounds), substances have been found, namely compounds [LXXII, R′ = R″ = H, R = 3-F, 3,4-$(OMe)_2$ or R = 4-OMe, R′ = Me, R″ = H], which exhibit a pronounced antiradiation activity,[60,65,66] The authors were unable to establish a relation between the rate of hydrolysis of these compounds, leading to the liberation of free MEA, and the radioprotective activity.[65,67] 2-(4- and 5-Benzo-2,1,3-thiadiazolinyl) derivatives exhibited a low level of protection.[12] A series of monosaccharide derivatives of thiazolidine have been described.[68]

Six-membered homologues of thiazolidines, namely perhydro-1,3-thiazines (LXXIII), containing alkyl and aryl substituents in the 2-position,[69] are of undoubted interest: among the 16 compounds of this series which have been synthesised, several highly effective radioprotectants (LXXIII, R = H, Ph, 4-FC_6H_4, 3-BrC_6H_4, or 2-MeC_6H_4) have been discovered. It has been observed that the RPE of the bases and the hydrochlorides are very different; thus, for R = Me, Pr, or 2-MeC_6H_4, the free bases show a much higher activity than the hydrochlorides, but, when R = 4-FC_6H_4 or 3-BrC_6H_4, the hydrochlorides are more effective.[69]

The RPE of several thiazolidines in which the carbon atom in the 2-position has been substituted by heteroatoms have been studied. In experiments on cell cultures[67] and on mice[70] it has been shown that germanium derivatives (LXXIV)[67,70] have higher RPE than all the thiazolidine derivatives investigated previously but are more toxic. Silathiazolidines exhibit a high RPE.[70]



(LXXIV)
R = H, Me; R′ = R″ = Alk
M = Ge, Si

(LXXV)

It has been shown that the anticancer preparation cyclophosphamide (LXXV) is inactive when introduced intraperitoneally 1–24 h before irradiation, but, when it is administered 2–4 days ahead, it protects 50% of the lethally irradiated animals.[71]

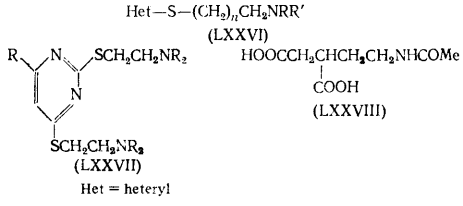
An unusual outcome of the search for radioprotectants in the thiazolidine series carried out in the previous period has been the establishment of correlations between the radioprotective activity and the calculated electron density at the sulphur and nitrogen atoms[72] and also structural factors (calculation by the Free–Wilson method).[73]

Thus, several substances with a high radioprotective activity have been found among fairly large numbers of thiazolidine derivatives synthesised and investigated.

7. Other Derivatives of Mercaptoalkylamines

This Section deals with compounds synthesised and investigated as potential radioprotectants whose structure is more remote from that of MEA and which were not included in the previous Sections. These are derivatives of mercaptoalkylamines with non-functional substituents at the sulphur atom and also with a modified hydrocarbon chain, including those where the chain is incorporated in a cyclic system or contains a carbonyl group.

Among the large group of *S*-heteryl-substituted mercaptoalkylamines (LXXVI),[74–79] the highest activity (up to 70–90% survival rate) was shown by compounds with hydroxypyrimidine[74] and quinazoline[74,78] rings as well as di-substituted pyrimidines (LXXVII).[74] The succinic acid derivatives (LXXVIII)[80] have a similar activity.

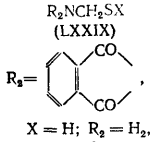


Het—S—$(CH_2)_nCH_2NRR'$
(LXXVI)

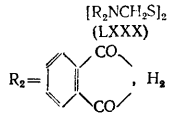
(LXXVII)
Het = heteryl

(LXXVIII)

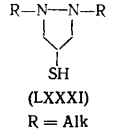
Derivatives of mercaptomethylamine (LXXIX) and (LXXX)[81] are of interest, but the results of biological studies are not presented in the relevant communication.



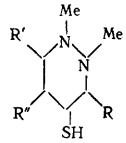
R_2NCH_2SX
(LXXIX)
X = H; $R_2 = H_2$,
$X = SO_3H$



$[R_2NCH_2S]_2$
(LXXX)



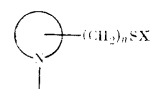
(LXXXI)
R = Alk



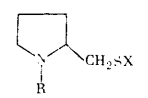
(LXXXII)

Another unusual group of mercaptoalkylamine derivatives are compounds in which the nitrogen atom is incorporated in a heterocyclic ring. Among compounds of the type of (LXXXI) and (LXXXII),[82,83] none have been found with radioprotective activity.

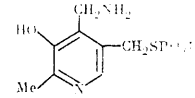
At the same time highly effective radioprotectants have been discovered among nitrogen-containing heterocycles in which the *S*-functional group is in the side chain, as in compound (LXXXIII):



(LXXXIII)



(LXXXIV)
$X = SO_3H, PO_3H_2, C(=NH)NH_2$
a) R = H, $X = PO_3H_2$;
b) R = Me, $X = PO_3H_2$



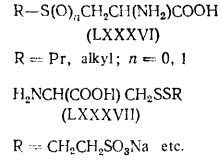
(LXXXV)

The heterocyclic system in these compounds is represented by the pyrrolidine [compound (LXXXIII)[35,36]], imidazole,[84] tetrazole,[11] pyridine,[85,86] pyrimidine,[87,88] and benzimidazole[87] rings.

Perhaps the most interesting result has been obtained in the study of the phosphorothioic derivatives (LXXXIV). It was shown[35] that compound (LXXXIVa) has a high RPE, while the replacement of the hydrogen atom by the methyl group, as in compound (LXXXIVb), entails the loss of activity.

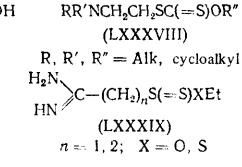
Comparison of the rates of hydrolysis of the phosphorothioate to the thiol and of the RPE for different time intervals between the administration of compound (LXXXIVa) and irradiation of mice led to the conclusion that there is no relation between these quantities. Pyridoxamine phosphorothioate (LXXXV) also gives rise to a high RPE.[86]

Derivatives of cysteine, namely esters,[62] sulphides and sulphoxides (LXXXVI),[89] and di- and poly-sulphides (LXXXVII)[90] have been synthesised as potential radioprotectors.



$R—S(O)_nCH_2CH(NH_2)COOH$
(LXXXVI)
R = Pr, alkyl; n = 0, 1

$H_2NCH(COOH)CH_2SSR$
(LXXXVII)
$R = CH_2CH_2SO_3Na$ etc.

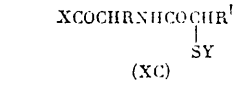


$RR'NCH_2CH_2SC(=S)OR''$
(LXXXVIII)
R, R′, R″ = Alk, cycloalkyl

(LXXXIX)
n = 1, 2; X = O, S

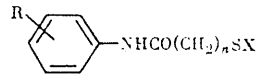
Among xanthates of the type of (LXXXVIII),[91] substances have been discovered which are superior to AET in terms of their RPE; it has been noted that some of them increase the survival rate of mice under the conditions of gamma-neutron irradiation; the amidino-derivatives (LXXXIX) are less active.

The summarising communication by Japanese investigators[92] quotes data concerning a large number of mercaptoalkanoylaminoacids (XC) investigated, which are analogues of mercaptopropionylglycine (XCa) (thiol, meprin, MPG) studied previously. Among them, only the amide (XCb) showed a pronounced radioprotective activity close to that of compound (XCa). Derivatives of MPG, namely compounds (XC, c and d),[93,94] the disulphide (XCe),[95,96] the thiosulphate (XCf),[97] and the phosphorothioate (XCg)[97,98] have been described as radioprotectants.



(XC)

a) X = OH, Y = R = H, R' = Me;
b) X = H_2N, Y = R = H, R' = Me;
c) X = OH, Y = R = H, R' = Alk, Ar, aryl alkyl;
d) X = OH, Y = H, R = Alk, $PhCH_2$, R' = Me;
e) X = OH, Y = SCH(Me)$CONHCH_2COOH$, R = H, R' = Me;
f) X = OH, Y = SO_3Na, R = H, R' = Me;
g) X = OH, Y = PO_3HNa, R = H, R' = Me



(XCI)

n = 1, 2; X = SO_3Na, C(=NH)NH_2

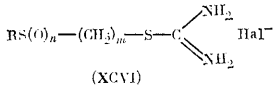
More remote analogues of MPG, among which mention should be made of the *N*-aryl derivatives (XCI)[88] and (XCII)[80,87,99] as well as the disulphides (XCIII)[100] and (XCIV)[101] and the hydrazide (XCV),[22] have also been investigated.

III. OTHER SULPHUR-CONTAINING COMPOUNDS

Apart from the compounds in which the aminoalkanethiol structure is repeated, sulphur-containing substances of different structure with or without nitrogen atoms in their composition have been synthesised and investigated in recent years as potential antiradiation agents.

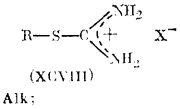
The synthesis of radioprotectants having the isothiuronium structure is traditional. Thus Japanese investigators achieved the synthesis of a series of isothiuronium derivatives (XCVI),[102] one of which has been obtained independently by Soviet workers.[103] A series of di-isothiuronium compounds (XCVII) have also been obtained independently by Japanese and Soviet investigators.[53,104,105] A satisfactory correlation between their physical properties and the RPE has been established.[104]

A study has been made of 34 compounds having the isothiuronium structure and containing an organophosphorus anion [compounds (XCVIII) and (XCIX)].[106-111] *S*-Ethylisothiuronium diethyl phosphate and metaphosphate as well as *S*-isopropylisothiuronium metaphosphate showed the highest RPE.[110]



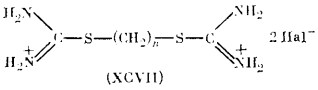
(XCVI)

R = H, Alk; m = 1, 2; n = 0, 2



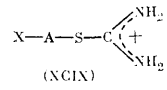
(XCVIII)

R = Alk;
X⁻ = anion of phosphorus-containing acid



(XCVII)

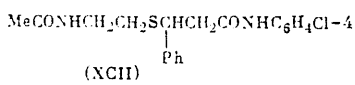
n = 2, 6



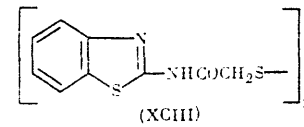
(XCIX)

A = alkylene or hydroxy-alkylene;
X = residue of phosphorus-containing acid

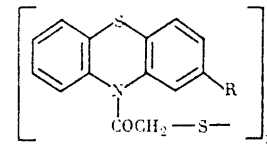
Arylisothiuronium derivatives (C) and (CI),[53,87,105] thiosulphuric acid derivatives (C),[87,99] and the disulphides (CII)[90] have been proposed as potential radioprotectants.



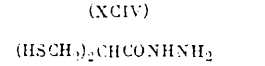
(XCII)



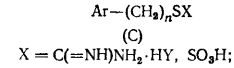
(XCIII)



(XCIV)

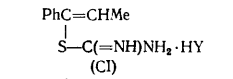


(XCV)

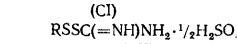


(C)

X = C(=NH)NH_2·HY, SO_3H; n = 1—3

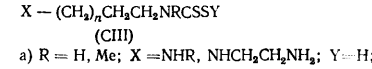


(CI)



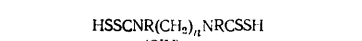
(CII)

R = $CH_2CH_2SO_3Na$, $CH_2CH(OH)CH_2SO_3Na$



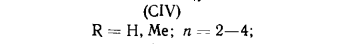
(CIII)

a) R = H, Me; X = NHR, $NHCH_2CH_2NH_2$; Y = H; n = 1, 3
b) R = H; X = SEt, SO_2Et; Y = Et; n = 0, 1;
R = Me; X = SEt; Y = Et; n = 0;



(CIV)

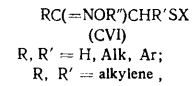
R = H, Me; n = 2—4;



(CV)

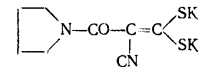
Substances with a distinct antiradiation activity have been discovered among derivatives of dithiocarboxylic acids (CIIIa), (CIV),[112,113] (CIIIb),[103] and (CV).[53,105]

Derivatives of 2-*N*-alkoxyiminoalkanethiols (CVI)[114] have been studied as radioprotectants, but they proved to be almost inactive.



(CVI)

R, R' = H, Alk, Ar;
R, R' = alkylene,
R'' = Me, Et;
X = COSEt, CSSEt, SO_3Na

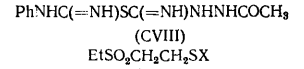


(CVII)

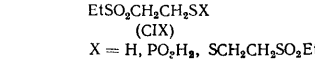
1-(3,3-Dimercapto-2-cyanoacryloyl)pyrrolidine (CVII)[27] afforded 80% protection to irradiated mice when administered enterally in a near-toxic dose, but its activity is low when it is administered orally.

Compounds (CVIII) containing the amidine fragment[115-117] exhibit a weak radioprotective activity.

As already stated, the search for prophylactic antiradiation agents has also been conducted among sulphur compounds not containing nitrogen, for example, among the alkyl derivatives (CIX), (CX),[103] and (CXI)[118] as well as aromatic and heterocyclic derivatives (CXII)[81,99] and (CXIII).[119]

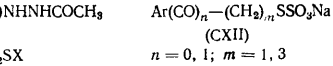


(CVIII)



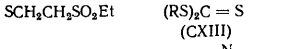
(CIX)

X = H, PO_2H_2, $SCH_2CH_2SO_2Et$

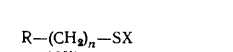


(CXII)

n = 0, 1; m = 1, 3



(CXIII)



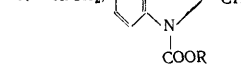
(CX)

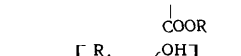
R = Ac, OEt; X = H, PO_3H_2, n = 1, 2

(CXI)



R = $ArCH_2$,





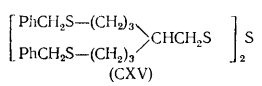
(CXIV)

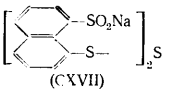
R, R', R'' = H, NO_2, Hal; n = 0—2

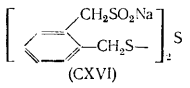
The sulphur-containing bisphenols (CXIV) exhibit a pronounced radioprotective activity[120] (when administered intra-abdominally 1 and 5 h before irradiation), but these data require additional checks, since the substances were introduced in the form of a solution in dimethyl sulphoxide, which is itself known to have a protecting activity.

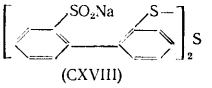
2,3-Dimercaptopropanesulphonic and dimercaptosuccinic acids or their potassium and sodium salts have been proposed as radioprotectants.[121]

5-Thio-D-glucose has been subjected in recent years to extensive studies as a radioprotectant for normal and tumour tissues.[39,122-124]


(CXV)


(CXVII)


(CXVI)


(CXVIII)

The continuation of studies initiated previously on the synthesis and radioprotective activity of a series of trisulphides yielded compounds (CXV)–(CXVII) having an aromatic structure;[34,125] compound (CXVIII) with LD_{50} of 430 mg kg^{-1} when administered intra-peritoneally almost fully protects mice in a dose starting from 4.6 mg kg^{-1}, while all the animals in the control group died.

This substance is less effective when administered orally. The introduction of chlorine atoms into the *meta*-positions relative to the sulphur atoms lowers the activity significantly. The phenyl and particularly the naphthyl analogues (CXVI) and (CXVII) are greatly inferior to the biphenyl compound (CXVIII) as regards activity.

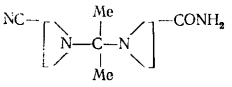
The attempt to find effective radioprotectants among selenium compounds were unsuccessful.[126-130]

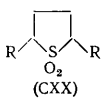
Thus, among sulphur compounds which do not belong to the series of mercaptoethyl derivatives, trisulphides containing residues of sulphinic acid, phosphorus-containing isothiuronium derivatives, and 5-thio-D-glucose are of greatest interest as potential radioprotectants.

IV. HETEROCYCLIC COMPOUNDS

Compared with previous years, there has been a marked growth of interest recently in heterocycles as potential radioprotectants. The main trends in the search for radioprotectants in this extensive branch of organic chemistry have been described in a review.[3]

2-(2-Cyanoaziridino)-2-(2-carbamoylaziridino)propane (CXIX), which ensures a 50% survival rate of mice when administered intra-peritoneally in a dose of 50 mg kg^{-1} two days before irradiation has been proposed for the prophylaxis and treatment of radiation damage.[131-133]

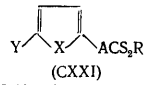

(CXIX)


(CXX)

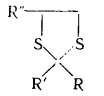
a) R=H; b) R=CH(OH)$CH_2CH_2CONR'_2$, R'=H, Me

It has been observed[134] that sulpholan (CXXa) and its bisbutyramide derivatives (CXXb) exhibit a pronounced radioprotective activity; they are actually superior to MEA (DCF = 1.6). A relation between the electron-donating properties of substances in this series and their radioprotective activity has been found with the aid of quantum-mechanical calculations.

A series of dithiocarbamate derivatives of furan and thiophen [compounds (CXXI)] have been investigated. Among them, only compound (CXXIa) showed a weak RPE, while the remaining compounds are inactive[135]


(CXXI)

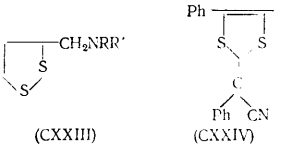
A=SO_2NH, R=Me, X=S, Y=H (a)
A=$C(CN)_2$, SONH; R=Alk, K; X=O, S; Y=H, Cl


(CXXII)

R=Alk, Ph, H; R'=Alk, Ar, Ac; R, R'=alkylene; R''=H, Alk

Continuation of earlier studies on the synthesis and the RPE of dithiolans by French investigators alone yielded 92 new derivatives of this class of heterocycles [compounds (CXXII)],[65] among which 32 afforded more than 50% protection to irradiated mice. It was impossible to establish general structure–activity relations, but certain partial conclusions can apparently be made. Thus the introduction of polar substituents into the 4-position (R'') and of aryl substituents into the 2-position (R) weakens the protecting activity; the presence of cycloalkyl substituents in the 2-position (R') promotes a decrease of activity.[136,137] Among 1,2-dithiolans (CXXIII),[138] effective radioprotectants have not been discovered.

Whereas 1,3-dithiolen (CXXIV)[27] does not exhibit radioprotective activity, there are data for the 1,2-dithio-derivative (CXXV)[139,140] showing that it has been used to protect the central nervous system of human beings against radiation in X-ray therapy.


(CXXIII) (CXXIV) (CXXV)


(CXXVI) (CXXVII)

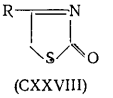
R=H, Me, SH; R'=H, Me; R, R'=alkylene; R'=H, CH_2Cl

R=H, R'=Alk, Ar; R, R''=alkylene; R''=H, Me

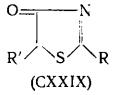
Among 19 1,3-oxathiolan derivatives (CXXVI),[66] 5-chloromethyl-1,3-oxathiolan-2-thiol showed the highest activity; the introduction of an aryl substituent in the 2-position results in a loss of protecting activity. In contrast to this, 1,3-oxazolidines (CXXVII)[65,141,142] exhibit an RPE only in the presence of an aryl substituent in the 2-position; the *m*-chlorophenyl derivative showed the highest activity.

Thiazolidine and 2-aminothiozoline derivatives were examined above.

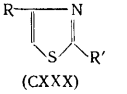
Among 4-hydrazinothiazolin-2-one derivatives (CXXVIII),[143] 5-alkyl-2-aminothiazolin-4-ones[144] and 5-alkyl-2-hydrazinothiazolin-4-ones (CXXIX),[143] compounds affording 30–60% protection to irradiated mice, were found.


(CXXVIII)

R=$NHNH_2$, $NMeNH_2$


(CXXIX)

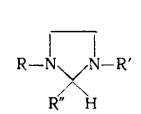
R=NH_2, $NHNH_2$, PhNHN=CH; R'=H, Me, Et, CH_2COOH


(CXXX)

a) R=2,4-$(HO)_2C_6H_3$, Ph; R'=NH_2,
b) R=*m*-ClC_6H_4, R'=NH_2

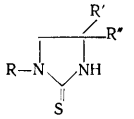
A fairly high RPE has been discovered for 2-amino-4-arylthiazoles, in particular the phenyl and 2,4-dihydroxyphenyl derivatives (CXXX);[145-147] the replacement of the amino-group by the hydrazino-group entails the loss of activity,[145] while incorporation of the hydrazino-group in the pyrazole ring sometimes almost fully restores the initial level of protection.[148,149] Comparison of the antioxidant properties of the dihydroxyphenyl derivatives (CXXXa) in relation to a model fat and the RPE enabled the authors to conclude that there is no relation between the ability of these compounds to inhibit free-radical processes and their radioprotective activity.[146]

Among 36 imidazolidines, the highest RPE has been found for the 2-(*p*-tolyl) derivative monomethylated at the nitrogen atom [compound (CXXXI)]; alkylation of the second nitrogen atom has an ambiguous effect.[66] Ethylenethiourea has no radioprotective activity, but, after the introduction of methyl groups both into the hydrocarbon chain and at the nitrogen atom, compounds with an appreciable RPE are produced (30–40% protection) [compounds (CXXXII)].[66]



(CXXXI)

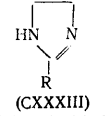
R, R′=H, Me; R″=Ar



(CXXXII)

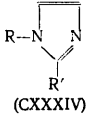
R=H, Me; R′, R″=H, Alk, Ar, R′, R″=alkylene

A deeper investigation of the RPE of imidazole and Naphthysin has been continued[113,115] together with the search for new radioprotectants among imidazoline and imidazole derivatives. In contrast to imidazolidine derivatives, 2-phenylimidazoline and its benzyl analogue (CXXXIIIa) proved to be inactive, while 2-imidazolidinethione (CXXXIIIb) protected 70–80% of the irradiated animals.[150] On passing to imidazoles, the 2-phenyl derivative (CXXXIV) again proved to be active.[150] Mono- and di-alkylimidazoles (CXXXIV) had a high RPE in experiments on mice,[150] while 4,5-diarylimidazolyl vinyl sulphides (CXXXV) proved to be relatively ineffective.[151]



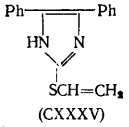
(CXXXIII)

a) R=Ph, $PhCH_2$;
b) R=OH, SH



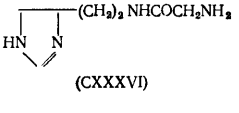
(CXXXIV)

R=Alk, H; R′=H, Me, Ph



(CXXXV)

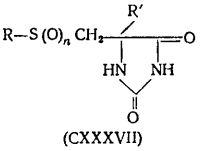
R=H, $CH=CH_2$



(CXXXVI)

A high radioprotective activity is observed after the subcutaneous administration of glycylhistamine (CXXXVI) to mice 24 h before irradiation and after intra-peritoneal administration 30 min before irradiation.[152] The substance administered intra-peritoneally becomes inactive after 24 h.

Interesting results have been obtained in the study of thiomethyl derivatives of hydantoins (CXXXVII); thus 5-propyl- and 5-allylthiomethyl-5-methylhydantoins (CXXXVIIa) are four times superior to cystine in terms of the test based on the survival of irradiated mice and by a factor of 2 in terms of the duration of their activity.[89,153] The replacement of the methyl group by hydrogen or the oxidation of sulphide sulphur to sulphoxide sulphur fully abolish the protecting activity of compounds (CXXXVII, b and c).[89,153]

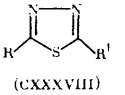


(CXXXVII)

a) R=H, Pr, $CH_2CH=CH$; R′=Me, $n=0$,
b) R=$CH_2CH=CH$; R′=Me; $n=1$,
c) R=$CH_2CH=CH$; R′=H; $n=0$.

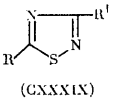
Familiar medicinal preparations derived from pyrazolone (antipyrine, amidopyrine, and analgin[154,155]) as well as 1-heterylpyrazolones and 1-heterylpyrazoles,[148,149] possess weak protecting properties.

It has been shown[75] that, in the presence of the amino- and mercapto-groups in the molecules of 1,3,4-thiadiazole (CXXXVIII) and 1,2,4-thiadiazole (CXXXIX), the level of protection in mice does not exceed 30%. It has been found[156] that the 5-amino-3-arylamino-1,2,4-dithiazolium salts (CXL) exhibit a moderate protecting activity, the presence of the methoxy-group in the benzene ring tending to increase the activity.

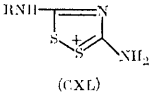


(CXXXVIII)

R = NR''_2; R′ = H, Me, SH, SMe

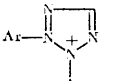


(CXXXIX)



(CXL)

R = H, Ar



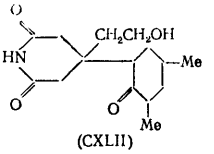
(CXLI)

The protecting effects of 5-mercaptomethyl-1,2,4-triazolin-3-one and 5-mercaptomethyl-1,2,4-triazoline-3-thione as well as the 2,5-diphenyl-1-phenylamino-1,3,4-triazolium salt are weak.[143]

Substances with a pronounced radioprotective activity have not been found among 5-substituted tetrazoles;[11] the water-soluble di- and tri-aryltetrazolium quaternary salts (CXLI), some of which, for example, compound (CXLI, R = Ar = Ph, X = Cl), protect up to 60% of mice irradiated with a lethal dose, are more promising in this respect.[157,158]

Thus highly effective radioprotectants belonging to the series of aryl derivatives of oxazolidines, thiazolidines, imidazolines, and thiomethylhydantoins have been found among five-membered heterocyclic compounds.

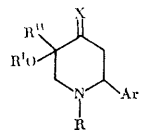
The search for radioprotectants among six-membered aromatic and non-aromatic heterocycles was less successful. Thus 3-hydroxy-2-methyl-4-pyrone (maketol)[159] does not protect irradiated mice.



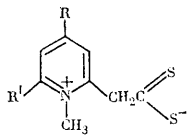
(CXLII)

Cycloheximide (CXLII) is of interest.[160] In experiments on rats it did not show a radioprotective activity when administered intra-abdominally directly before irradiation, but, when introduced in a dose of 2 mg kg^{-1} 6 and 12 h before irradiation, it effectively protected the skin and radiosensitive tissue. This compound is particularly attractive because it protects selectively normal tissues but not tumours.

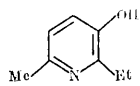
The structures of the piperidines and pyridines which have been investigated as potential radioprotectants but showed a low protecting activity or none at all are presented below:



R = Me, $PhCH_2$;
R^I = H, Ac; R^{II} = H, Me;
X = O, HOH (Ref.161)



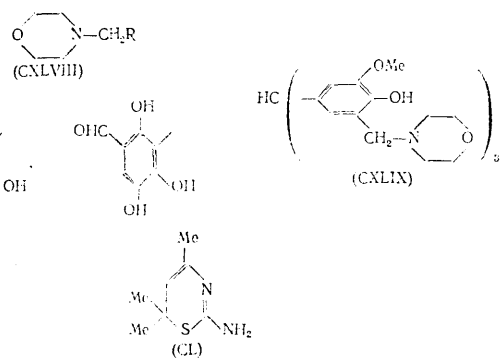
R = H, Me;
R^I = H, CH_2CSSNa (Ref.162)



(Ref.163)

Pyridinecarboxylic acids and their derivatives have been proposed as radioprotectants.[15] Nicotine bitartrate increases the lifespan of both young and old irradiated rats;[164] the possibility of using it in X-ray therapy is being considered.

Among six-membered heterocyclic compounds containing two heteroatoms, the Mannich bases (CXLVIII)[165] and (CXLIX),[166] which contain morpholine in their composition, exhibit a pronounced RPE. Thiomorpholine derivatives have been proposed as radioprotectants.[167,168]



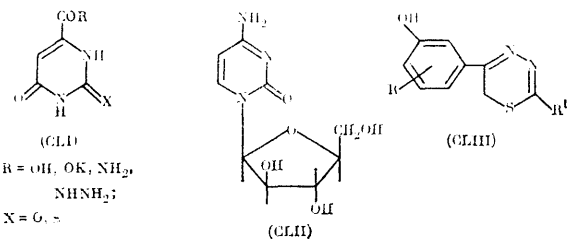
(CXLVIII)

(CXLIX)

(CL)

In the series of six-membered heterocyclic compounds with two heteroatoms, a pronounced antiradiation activity has been discovered only for 2-amino-4,6,6-trimethyl-1,3-thiazine (CL).[169]

A low level of protection against radiation or its total absence have been noted in a series of tetrahydro-derivatives of 2-amino- and 2-mercapto-1,3-oxazines[170] and the corresponding 1,3-thiazine[170,171] and pyrimidine[171] derivatives, the 2-thiones of hexa- and tetra-hydropyrimidines,[53,172] and also certain sulphur-containing derivatives of pyrimidine[135,162,173] and 2-amino-5-bromo-4-hydroxy-6-phenylpyrimidine.[39]



(CLI)

R = OH, OK, NH_2, $NHNH_2$;
X = O, S

(CLII)

(CLIII)

Two groups of investigators observed independently the high RPE of orotic acid and some of its derivatives (CLI).[174,177]

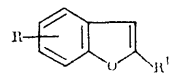
The familiar cytostatic compound cytosine arabinoside (CLII) does not protect mice when administered intra-abdominally 15–60 min before irradiation, but, when it is administered 48–72 h prior to radiation, the survival rate of mice irradiated with a lethal dose is 90%.[178]

A pronounced radioprotective effect has been observed for certain derivatives of 2-methylmercapto-1,3,4-thiadiazine (CLIII).[146] *sym*-Diphenyltetrazine and its 1,2-dihydro-analogue proved to be inactive.[143]

Thus, among six-membered heterocyclic compounds, derivatives of orotic acid and cytosine arabinoside are of greatest interest.

Among heterocyclic compounds investigated as potential radioprotectants, condensed systems and in the first place benzoheterocycles occupy a notable place.

2-Acetyl-6-methoxybenzofuran exhibits the highest RPE (70% survival rate) among the 14 benzofurans (CLIV) synthesised.[179]



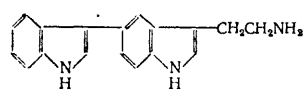
(CLIV)

R = H, OMe; R^I = H, CHO, Ac, CN, COOEt

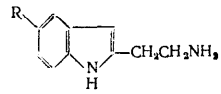
Indole derivatives are important among condensed heterocycles. The search for radioprotective agents in this series of compounds has been conducted mainly in two directions, i.e. via the modification of the tryptamine molecule (in the side chain or in the benzene ring) and via the synthesis of compounds with a non-tryptamine structure.

It has been shown[180] that tryptamine containing the indole substituent in the 5-position, as in compound (CLV), is superior in its radioprotective activity to the initial tryptamine but is inferior to mexamine.

5-Substituted isotryptamines (CLVI) proved to be weakly active.[181]

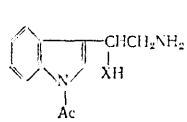


(CLV)

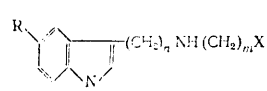


(CLVI)
R=H, Me,Cl, OH

Much attention has been devoted to the synthesis and investigation as possible radioprotectants of sulphur-containing derivatives of tryptamine and serotonin.[182–187] They are considered here and not in the previous Sections, since their indole structure in all probability plays the main role in their radioprotective activity. The synthesis of β-mercaptoethylamine and its *S*-functional derivatives (the sulphide, disulphide, sulphonate, and thiosulphate) with the indole substituent at the carbon atom [compound (CLVII)] did not lead to compounds with an appreciable radioprotective activity with the exception of compound (CLVII, R = H), which exhibits an RPE somewhat superior to that of tryptamine. A series of compounds in which the hydrogen atom in the amino-group of tryptamine or mexamine has been substituted by mercaptoalkyl groups [compounds (CLVIII)] have been synthesised.[183,184]



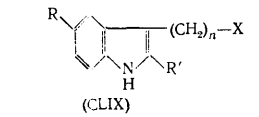
(CLVII)
X = SH, SO_3H, SSO_3H



(CLVIII)
R = H, MeO; n = 1, 4; m = 2, 3;
X = SH, SSO_3H, SPO_2H_2, $NHCH_2CH_2SH$

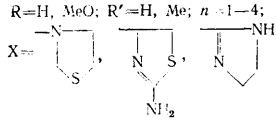
However, none of them has advantages as a radioprotectant relative to the initial unsubstituted amines. Analogous results have been obtained for 3-heterylalkyl-indoles and their 5-methoxy-derivatives (CLIX).[184,186]

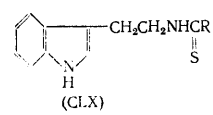
Thioamides containing the tryptamine residue (CLX) exhibt a high RPE.[185]



(CLIX)

R=H, MeO; R′=H, Me; n = 1—4;

X = 

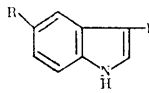


(CLX)

R=Me, Ph, $PhCH_2$

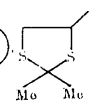
It has been shown[188] that the RPE of a series of 3-indolylalkylamines is correlated with the electron-donating activity calculated by quantum-mechanical methods.

Attention has been given to indole derivatives without the aminoethyl group in the 3-position. Among a large number of 5-alkoxy- and 5-acetyl-substituted compounds (CLXI) as well as 3-carbonyl derivatives of indole (CLXII), substances with a moderate protecting activity have been discovered.[189] The absence of a pronounced radioprotective activity has been demonstrated for a series of 2-amino- and 4-, 5-, and 6-aminoethyl-indoles.[185,190]

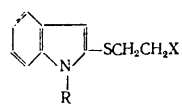


(CLXI): R = MeO, OMe, $PhCH_2O$; R′ = H

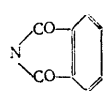
(CLXII): R = H; R′ = Ac, PhCO, C(SMe)=N⁺ I⁻

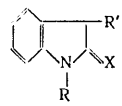


Indoles containing the mercaptoethyl functional group in the 2-position of the ring, as in compound (CLXIII),[185] exhibit a moderate RPE. Among indolinones, only the thio-derivative (CLXIV) shows a moderate radioprotective activity.[185]



(CLXIII)

X = NH_2, 

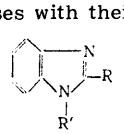


(CLXIV)

R=H, Me; R′=CH_2CN, CH(CN)COOH, $CH_2CH_2NH_2$; X=O, S

The search for radioprotective substances among derivatives of 2-aminobenzothiazole did not lead to compounds with an appreciable radioprotective activity.[147,169,191]

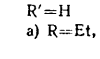
Certain other bicyclic heterocycles have been shown to exhibit an antiradiation activity. It has been stated[150,192] that a series of 2-alkyl- and 2-arylalkylbenzimidazoles (CLXV) exhibit a fairly high protecting activity in mice, which depends on the degree of lipophilicity of the molecule. The ethyl and *p*-chloro-α-hydroxybenzyl substituents [compounds (CLXV, a and b)] proved to be optimal; it is of interest that the toxic *o*-chloro-analogue shows no radioprotective activity.[150] It has been found that the toxicity of the compounds increases with their activity.



(CLXV)

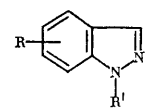
R=Alk, Ar, aryl alkyl;

R′=H

a) R=Et, b) R=

On the other hand, no appreciable protective activity has been observed for a whole series of benzimidazole derivatives with unsaturated and sulphur-containing substituents[151] and also *NN′*-dimethylbenzimidazolines and benzimidazolium salts.[79]

Interesting results have been obtained by a group of French investigators in a study of 23 compounds of the indazole series [compounds (CLXVI)].[193] They discovered that 6-nitroindazole (CLXVIa), administered in a dose corresponding to one half of LD_{50}, protects up to 90% of mice when administered intra-peritoneally 10 min before irradiation, while the 7-nitro- and 1-(*p*-chlorobenzoyl)-5-nitro-derivatives (CLXVI, b and c) ensured 70—80% protection of the animals when administered in a dose corresponding to one quarter of LD_{50}.

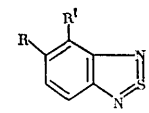


(CLXVI)

a) R = 6-NO_2, R′ = H

b) R = 7-NO_2, R′ = H

c) R = 5-NO_2; R′ = *n*-ClC_6H_4CO



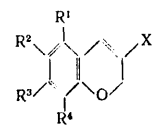
(CLXVII)

R = H; R′ = OH, NH_2, MeNH, Me_2N;

R = R′ = NH_2

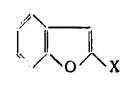
Extensive studies designed to find radioprotectants among benzo-2,1,3-thiadiazoles (CLXVII)—synthetic substitutes for a group of vitamins K [12,194–199]—made it possible to discover compounds with a pronounced antiradiation activity. These are in the first place the 4-hydroxy-, 4-amino-, 4-methylamino-, 4-dimethylamino-, and 4,5-diamino-derivatives.

Among the large group of 2*H*-chromenes (CLXVIII), substances have been found with a high radioprotective activity; the results for some of these are listed in Table 4.[179–200] The study of the comparative RPE of 2*H*-chromenes (CLXVIII) and benzofurans (CLXIX) containing identical substituents showed that the former have a more pronounced protective activity.



(CLXVIII)

X = CHO, Ac, CN, COOEt



(CLXIX)

Table 4. The radioprotective activity of compound (CLXVIII)[179] (intra-peritoneal administration to mice, 900 R γ-irradiation).

R¹	R²	R³	R⁴	X	LD_{50}, mg kg⁻¹	% protection		*I*
						for MTD*	for 1/4 LD_{50} dose	
H	H	OMe	H	CHO	600	60	50	6
H	H	H	H	MeCO	1000	40	80	7.2
H	H	OMe	H	MeCO	1000	80	60	6.4
H	H	H	OMe	MeCO	1000	100	50	6
OMe	H	H	H	MeCO	1000	30	70	6.8

*MTD = maximum transferable dose.

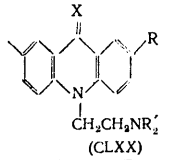
It has been reported[159,201–206] that many flavanoid compounds exhibit a pronounced radioprotective activity, but highly effective radioprotectants have not been discovered among them.

The vinyl derivatives of quinoline and its *N*-oxide,[207] derivatives of *N*-methylquinolinium and isoquinolinium containing the dithioacetic acid residue,[162] and *N*-acylaminoisoquinolinium salts[143] showed a low protecting effect in experiments on mice. Studies designed to find radioprotectants have been carried out among sulphenylamides and sulphides derived from quinoline and its *N*-oxide,[87,172,208-210] quinoxaline,[211] and 1,2-dihydrophthalazine,[212] but data on their activities are not quoted.

Apressin, which is a familiar medicinal preparation consisting of 1-hydrazinophthalazine,[155] protects 26.6% of the irradiated mice, while diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2-one) not only increases somewhat the survival rate of mice but also diminishes the toxicity of MEA.[213]

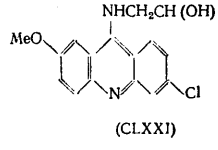
More complex benzoheterocyclic compounds have been subjected to radiobiological investigations to a much lesser extent.

Substances protecting more than 50% of the animals could not be found among *N*-substituted acridones (CLXX).[241] Acranil (CLXXI), an inductor of interferon, inhibits approximately the same effectiveness.[215]



(CLXX)

R=H, Cl, Br; R'=Me, Et; X=O, S



(CLXXI)

Thus certain indazole and chromene derivatives showed the highest radioprotective activity among benzoheterocyclic compounds.

In the series of condensed heterocyclic compounds, much attention has been devoted, as in the preceding period, to derivatives of purine and particularly adenosine. Substances with a moderate RPE have been discovered among sulphur-containing purine derivatives (CLXXII)[76] and (CLXXIII).[216] 2,6-Dimercaptonebularine has been described as a radioprotectant.[217] The absence of radioprotective activity has been noted for purine-8-thione and pyrido[2,3-*d*]imid-2-azolinethione.[135]

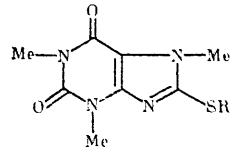
It has been found[218,219] that inosine (CLXXIV) exhibits a low protective activity, which is shown more distinctly when administered to small laboratory animals several days before irradiation. An increase in the survival rate of the irradiated mice has been observed after the prophylactic administration of certain 6-substituted adenosines.[220-222] The *p*-hydroxyphenylethyl and the indol-3-ylethyl derivatives (CLXXV) proved to be the most effective. It has been suggested[221] that the RPE of substances of this series is achieved via two pathways—via direct action at the cellular level and indirectly by virtue of the cardiovascular hypoxia induced by them. It has been shown[219,223] that the monophosphates of purine nucleosides exhibit a radioprotective activity and that their combination with ATP and sulphur-containing radioprotectors has a DRF = 2.[223] A review devoted to the mechanisms of the radioprotective activity of adenine compounds constitutes a kind of summary of studies on these lines.[224]

A clinical application of *S*-adenosylmethionine (CLXXVI) in X-ray therapy has been reported.[225]

The alkaloid emetin, which is an inhibitor of protein synthesis, exhibits a pronounced protecting activity when administered intra-peritoneally in a dose of 6.5 mg kg^{-1} 6–12 h before irradiation but not directly before irradiation.[160] The medicinal drug methotrexate also affords no protection when administered directly before irradiation, but provides 80% protection in mice when administered 24–48 h prior to irradiation.[178]

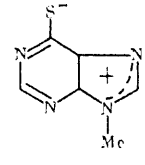
Derivatives of α-carboline proved to be ineffective.[197] The radioprotective properties of nalidixic acid (CLXXVII) have been reported.[226]

Detailed study of various types of synthetic porphyrins and their metal complexes showed[227-231] that among them there are compounds with a moderate RPE. This applies primarily to the *meso*-derivatives of aetioporphyrin-1 (CLXXVIII) and the tetra-alkyl ether-esters of haematoporphyrin (CLXXIX).

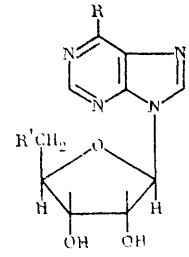


(CLXXII)

R = H, CH_2CH_2OH

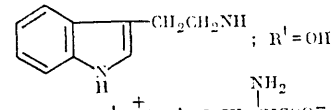


(CLXXIII)



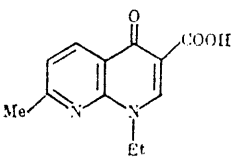
(CLXXIV): R = R' = OH

(CLXXV): R = *n*-$HOC_6H_4(CH_2)_2NH$,

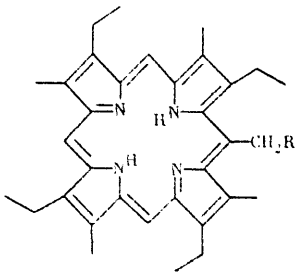


; R' = OH

(CLXXVI): R = NH_2, R' = $\overset{+}{S}(Me)CH_2CH_2\underset{NH_2}{\underset{|}{C}}HCOO^-$

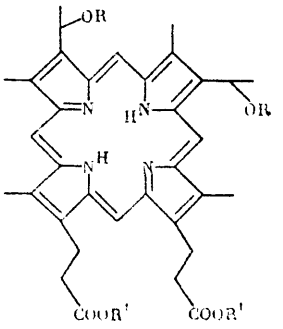


(CLXXVII)



(CLXXVIII)

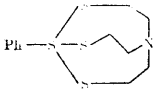
R = NHMe, NMe_2, MeO, $NH(CH_2)_2COOH$



(CLXXIX)

R = Alk, R' = H, Alk

It has been observed[232] that the acetylbenzoyl derivatives of the polycyclic alkaloid aconine is somewhat inferior in its radioprotective activity to MEA and AET. The silicon-containing heterocycle (CLXXX) has been proposed as a radioprotectant.[233]



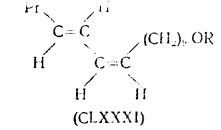
(CLXXX)

It follows from the data presented that substances with a high radioprotective activity have been discovered among heterocyclic compounds of different structure, which shows that further search for radioprotectants among them is promising.

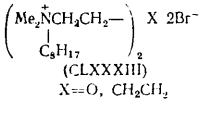
V. COMPOUNDS OF DIVERSE STRUCTURE

In this Section we shall consider aliphatic, aromatic, aliphatic-aromatic, and also certain phosphorus-containing compounds.

Isobombykol and its esters (CLXXXI) exhibit a high radioprotective activity.[234] Tests on a large number of patients showed that the prophylactic administration of *O*-alkylglycerols (CLXXXII)[235] diminishes the number of patients contracting radiation sickness in X-ray therapy.

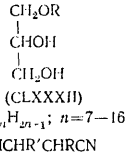


(CLXXXI)



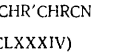
(CLXXXIII)

X=O, CH_2CH_2



(CLXXXII)

$R=C_nH_{2n-1}$; $n=7-16$



(CLXXXIV)

R, R', R''=H, Alk

Among other glycerol derivatives, 16 lipids and phospholipids of different structure have been studied, but effective protectors have not been found among them.[236] Nor have satisfactory antiradiation agents been found among different derivatives of amines, hydroxyamines, and diamines;[21] ethylenediamine[21] and quaternary salts of the type of (CLXXXIII),[10] which exhibit a pronounced RPE, are exceptions.

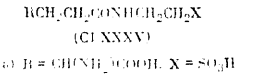
When administered in a dose of 30 mg kg^{-1} to mice, acetyl-β-methylcholine has a DRF = 1.27.[237]

The radioprotecting activity of β-aminonitriles (CLXXXIV) has been reported.[238,239]

Aminoacid derivatives continued to attract the attention of investigators. In particular, it has been shown[240] that potassium and magnesium aspartates administered to mice with food increase their survival rate and stimulate cell proliferation and differentiation in the thymus, spleen, and bone marrow.

Among the series of aminoacid protease inhibitors, only antipain increases somewhat the survival rate of mice.[24]

In recent years careful studies have been made of γ-*L*-glutamyltaurine (litoralon) (CLXXXVa), which was isolated from natural sources and subsequently synthesised and which exhibits a vitamin A-like activity.[242-250] This virtually non-toxic compound ensures a 50% survival rate of animals when introduced intra-peritoneally into mice in a dose of 100 mg kg^{-1} 4 days before irradiation. γ-Aminobutyryltaurine and its phosphorus analogue (CLXXXV, b and c) exhibit an analogous activity.[246-248]

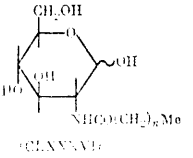


(CLXXXV)

a) R = $CH(NH_2)COOH$, X = SO_3H

b) R = CH_2NH_2, X = SO_3H

c) R = CH_2NH_2, X = $PO(OH)_2$



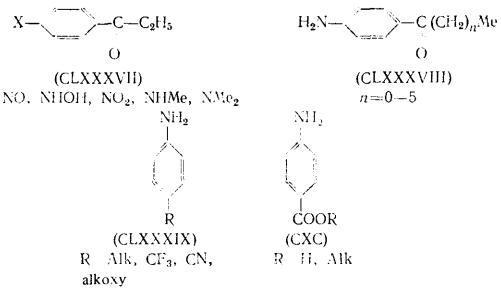
(CLXXXVI)

Certain disacharride derivatives with a low toxicity have been proposed as radioprotectants, but their RPE is low.[251,252] *N*-Acylated D-glucosamines (CLXXXVI), particularly those with $n = 8-12$, administered to mice in a dose of 0.05 mg kg^{-1} 2 days before irradiation, exhibit a high RPE.[253,254] A disadvantage of these substances is that they are virtually insoluble in water.

Thus aminoacid derivatives and, in particular litoralon, proved to be the most interesting among aliphatic compounds.

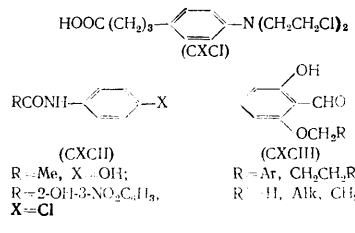
Since the 1950's, attempts have been made to employ antioxidants to protect the organism against the effects of radiation. During this period, studies have also been made of phenolic antioxidants used in the food industry, in particular of 2,6-di(t-butyl)-4-methylphenol,[255,256] but the degree of protection proved to be low.

Studies have continued on the radioprotective properties of derivatives and analogues of *p*-aminopropiophenone (CLXXXVII).[257] The influence of substituents on the RPE of compounds (CLXXXVII)–(CXC) has been investigated and it has been found that the aniline derivatives (CLXXXVIII, $n = 3$ and 4), (CLXXXIX, R = CF_3 or CN), and (CXC, R = Me or Et) have a somewhat higher activity than the parent *p*-aminopropiophenone.



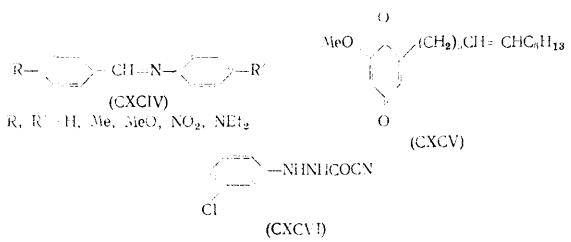
When administered in a dose of 12 mg kg^{-1} 72 h before irradiation, chlorambucil (CXCI) ensures a 65% survival rate of mice.[178]

The anilides (CXCII) investigated proved to be relatively ineffective.[258,259]



The ethers of 2,6-dihydroxybenzaldehyde (CXCIII) have been proposed as radioprotectants.[260]

The radioprotective activity of a series of azomethines (CXCIV) has been investigated.[261] They exhibited only a weak antiradiation activity; a semiempirical calculation by the Hückel LCAO-MO method yielded a satisfactory correlation between the electron-donating properties of the compounds and the RPE.[261] The azomethines based on trihydroxybenzaldehydes proved to be more effective:

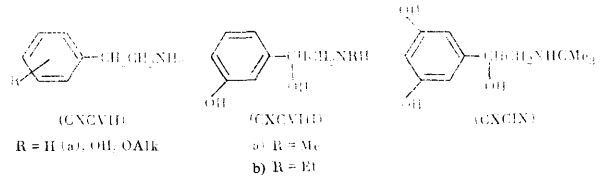


Among quinone derivatives, irisquinone (CXCV) has been proposed as a radioprotectant.[263]

The studies on organic derivatives of hydrazines have been continued: the data for the RPE of (3-chlorophenyl)hydrazino-oxoacetonitrile (CXCVI), which is an energy metabolism inhibitor, are contradictory,[264,265] while the medicinal preparation phelazine(2-phenylethylhydrazine) has a low activity.[155]

Considerable attention has been devoted during the period under consideration to phenylethylamine derivatives (CXCVIIa). Among compounds unsubstituted in the benzene ring, 2-amino-1-phenylethanol is the most active.[21,31]

More than 30 *o*-, *m*-, and *p*-hydroxy and *o*-, *m*-, and *p*-alkoxy-phenylethylamines (CXCVII) have been investigated, but no substances have been discovered among them which would increase the survival rate of the irradiated mice by more than 40%.[266] The replacement of the amino-group by the amido-, carbamido- and hydantoin groups decreased the toxicity but did not increase the RPE.[267]



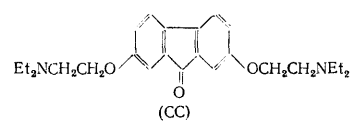
The introduction of the hydroxy-group in the β-position of *m*-hydroxyphenylethylalkylamine increases sharply the radioprotecting activity.[21,268–272] The *N*-methyl derivative (mezaton) and also the *N*-ethyl derivative (phetanol) [compounds (CXCVIII, a and b)] (25–50 mmol kg^{-1}) exhibit a stable RPE combined with a low toxicity (LD_{50} = 4.8 mmol kg^{-1}) when administered to mice subcutaneously (s/c) and intra-peritoneally. It has been shown[268,269] that the ED_{50} for the laevorotatory *S*-isomer of mezaton (CXCVIIIa) is lower almost by a factor of 2 than for the racemate (8.3 and 13 mol kg^{-1} respectively). It has been found that the *ortho*- and specially the *para*-hydroxy analogues of compound (CXCVIIIa) are less active.[269,272] The level of protection is reduced after the introduction of an additional hydroxy-group into the molecule of compound (CXCVIIIa) in the 4- or 6-position of the benzene ring.[269,270] The replacement of hydrogen in the amino-group by more bulky substituents, for example the adamantyl[269] or carbamido-groups,[267] leads to the loss of the RPE.

At the same time, the use of the β-sympathomimetic compound terbutaline (CXCIX) as a radioprotectant in the X-radiotherapy of tumours has been mentioned.[273]

Esterification of the phenolic hydroxyl or its substitution by the toluene-*p*-sulphonamide residue in compound (CXVIIIb) lowers the RPE.[269] 2-Amino-1-β-naphthylethanol proved to be inactive.[182]

Thus derivatives of arylalkanolamines are not inferior to aminothiols and indolylalkylamines as regards their RPE, being actually superior to them in terms of the width of their activity spectrum and the low optimum effective dose required,[268] but they suffer from the disadvantage that they give rise to a sharp and prolonged increase in blood pressure.[270]

The mechanism of the protection afforded by these compounds has not been ultimately elucidated. There exist convincing data showing that their action is associated with induced circulatory hypoxia,[31,270,271] but experimental data such as the lack of a decrease of the partial O_2 pressure in the liver and spleen when radioprotective doses of mezaton are used,[269] the presence of a protecting effect at the cellular level,[274,275] and the concentration-dependent influence of adrenolytic compounds on RPE[276,277] show that protection by these compounds can be achieved by their direct action on the cells. The radioprotective activity of sympathomimetic compounds is apparently realised via both a pharmacological pathway (indirectly) and at the cellular level; depending on the structure of the radioprotectant, the relative contributions by these pathways can vary.



Tilorone (CC), which is a familiar interferon inductor, gives rise to a cyclic type of enhancement of the resistance of animals to radiation; thus, when administered to mice intra-peritoneally 15–30 min before irradiation, it gives rise to a pronounced RPE, after 3 h it is completely ineffective, and after 6 h its protection again reaches the initial

level. Satisfactory results have been obtained when compound (CC) was administered 2–3 days before irradiation.[215,273]

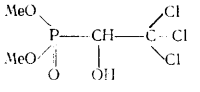
Steroids with a wide variety of structures have been used to increase the resistance of animals to radiation (see, for example, Refs.178, 279–285), but effective radioprotectants have not been discovered among them and furthermore these compounds were frequently administered to animals repeatedly over a fairly long period.

Various vitamins continue to attract the attention of radiobiologists but their protecting effect does not as a rule exceed an amount corresponding to a 30–40% survival rate.[286–292]

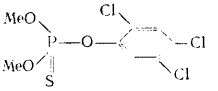
The results of studies of the radioprotective effect of vitamin K (ubiquinones) on mice merit attention. They proved effective when administered intra-peritoneally 10 h before irradiation.[292]

The demonstration of a high DRF in experiments on rabbit erythrocytes on treatment with riboflavin (DRF = 4.0), vitamin B_{12} (DRF = 3.6), and cytochrome *c* (DRF = 4.7) is also noteworthy.[291]

It has been found that penicillin exhibits a low radioprotective effect.[293]



(CCI)



(CCII)

The radioprotective activity of the organophosphorus compounds chlorophos (CCI) and trichlorometaphos (CCII) has been investigated in detail. When administered intraperitoneally 3 h before irradiation, they afford protection to rats (DRF = 1.18 and 1.42 respectively).[294–299] These substances show a higher RPE when combined with dianabol and MEA.[297]

Thus, among aromatic and other compounds examined above, derivatives of phenylalkanolamines, which exhibit a high RPE and a broad therapeutic spectrum, have attracted attention.

Summarising, certain conclusions can be drawn. The number of publications devoted to the search for prophylactic radioprotective agents has increased somewhat, but the number of substances investigated (per annum) diminished somewhat, which applies in the first place to compounds with the aminothiol structure. A new class of highly effective radioprotectants, namely derivatives of arylalkanolamines, has been discovered. The relative contribution of heterocyclic compounds as potential radioprotective agents has greatly increased. It has been shown that thiazolidine derivatives are not unique among heterocyclic compounds as appeared to be the case previously; dithiolans and oxazolidines possess approximately the same activity. Other highly effective compounds, for example, chromenes and orotic acid derivatives, have been discovered.

For the first time, it has become possible to speak with confidence of the possibility of the practical application of radioprotectants. This has been confirmed by clinical studies on several preparations simultaneously, namely gammaphos, meprin, 5-thio-D-glucose, and terbutaline, in the prophylactic treatment designed to afford protection against radiation damage in cancer X-ray therapy.

A particularly vigorous search for new radioprotectants is to be expected in the next few years among heterocyclic compounds, arylalkanolamines, and aminothiol derivatives containing functional groups. This will be assisted by the data obtained in recent years demonstrating high RPE values for certain substances and data concerning the relation between structure and activity in various series of organic compounds.

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During the preparation of the manuscript for the press, several communications concerned with the search for radioprotective substances were published. The salts of adenosine 5'-monophosphate with MEA and cystamine have been investigated as radioprotectors;[300–303] *N*-adamantoylmercaptoethylamine proved to be relatively inactive.[304] Among the *S*-2-thiazoline[305] and *S*-2-furfuryl[306] derivatives of MEA, the latter showed a high RPE; the replacement of the amino-group by the amidino- or guanidino-group does not increase the activity.[306] Effective substances in the series of *N*-adamantyl derivatives of gammaphos and its analogues have not been discovered.[304] It has been found that, among derivatives of compounds (XXXV) and (XLVI) substituted at the nitrogen atom by aryloxyalkyl and arylalkyl groups, the highest activity is shown by *S*-2-[4-(5-methoxy-3-methylphenoxy)butylamino] ethylthiosulphuric acid.[307]

The preparation adeturon described above has been recommended for clinical tests in X-radiotherapy.[301,303,308] The adamantyl and adamantoyl derivatives of AET proved to be relatively inactive.[304] In contrast to the data recorded above concerning the relation between structure and activity, a correlation has been reported between the period of the radioprotective activity of 2-phenyl- and 2-*m*-bromophenyl-thiazolidines and their metabolism.[309] It has been shown that halogenoalkylisothiuronium salts exhibit a moderate RPE.[310]

The results of studies of the radioprotecting activity of sodium diethyldithiocarbamate have attracted attention: following its intra-peritoneal administration to mice 30 and 120 min before irradiation in a dose of 1000 mg kg^{-1}, the DRF = 1.5–1.6 was attained (for a dose of 335 mg kg^{-1} of the same substance, Bacg et al.[311] achieved 40% protection); sodium diethyldithiocarbamate has been recommended for clinical tests in X-ray therapy.[312–314]

Highly effective radioprotectors have been found among nitrogen-containing aromatic heterocyclic compounds with the mercapto-group in the side chain. The highest activity is shown by 2-mercaptomethylpyridine and the corresponding phosphorothioate (the *N*-oxides and 2-pyrazinylmethylphosphorothioic acid are somewhat inferior to them) as well as all the mercaptopyridine isomers.[315]

The radioprotective properties of alkyl 2-furyl and alkyl 2-pyranyl sulphides have been investigated.[316] Effective radioprotectants have not been discovered among pyridazine and pyridazine-3,6-dione derivatives.[317] Salts of mexamine with adenosine 5'-phosphates, which are more active than mexamine itself, have been obtained and investigated.[318] It has been shown that 1-β-hydroxyethyl-5-nitro-2-phenacylthiobenzimidazole[319] and certain xanthine, adenine, 8-aza-adenine, and 2-thio-8-aza-adenine derivatives which have been investigated[320] exhibit a weak protecting activity.

Among other bicyclic and tricyclic nitrogen-containing heterocycles of the quinoline[321] and azepine[322] series, derivatives of tetrahydro-1*H*-pyrido[3,2-*b*]azepine and tetrahydro-1*H*-pyrido[2,3-*b*]azepinone showed a high RPE.[322] The results of the primary selection from a series of synthetic porphyrins, namely derivatives of deuterioporphyrin (IX), mesoporphyrins IX and II, aetioporphyrins I and II, and coproporphyrin I (77 compounds in all), have been published.[323]

Interesting results have been obtained in the study of sulphur-containing sugars as radioprotectants.[324] Thus 6-thio-D-fructose (LD_{50} = 17.5 g kg^{-1}) administered intra-abdominally to rats in a dose of 500 mg kg^{-1} 30 or 120 min before irradiation ensured a 100% survival rate of the animals, whereas all the control animals died. The protective effect persists also if the compound is administered 6 h before irradiation.[324]

Among other substances of natural origin, radioprotecting activity has been observed for the tetrapeptide taftsin,[325] the polypeptide melittin,[326] and also the natural prostaglandin E_2 and its synthetic analogue 1,6-dimethylprostaglandin E_2.[327]

In the series of aromatic amines (*o*-toluidine derivatives), substances with radioprotective activity were not found.[322] A pronounced radioprotective activity of certain antihelminthic preparations has been reported,[328] namely 3,5-dibromo-*N*-[4-chloro-3-(4-chlorobenzoyl)phenyl]-2-hydroxybenzamide (tetalid [sic]) and 3,5-di-iodo-*N*-[4-chloro-3-(2,5-dimethylbenzoyl)phenyl]-2-hydroxybenzamide, but these data require confirmation, since the compounds were administered to the animals in solution in dimethyl sulphoxide, which itself exhibits a radioprotective activity.

As a supplement to the data discussed in the review, references may be made to studies devoted to the radioprotective effect of ubiquinones,[329] vitamin B_{12} and folic acid,[330] *N*-substituted 2-amino-1-*m*-hydroxyphenylethanols,[331] and the nitriles of cinnamic and hydrocinnamic acids.[332]

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