The low toxicities of the novel pyrimidines (II) and (IV) and their activities indicate the desirability of further studies of compounds of these types as potentially biologically active agents.

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SYNTHESIS AND RADIOPROTECTANT PROPERTIES OF SOME S-SUBSTITUTED BIS-(2,2'-MERCAPTOETHYL)AMINES

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It has been found over the last three decades that some of the most active antiradiation agents are aminothiols and their S-derivatives, for example thiophosphates, thiosulfates (Bunte salts), isothiuronium salts, etc. [1, 3, 5, 9, 10].

We here describe the synthesis and examination for radioprotectant activity of the 2,2'-bisthiophosphato- (I), bisthiosulfo- (II), and bisisothiuronium (III) derivatives of dimethylamine.

The compounds were obtained by reacting bis-(2-bromoethyl)amine hydrobromide with Na_3SPO_3, $Na_2S_2O_3 \cdot 5H_2O$, or $SC(NH_2)_2$, as follows:

$$HN(CH_2CH_2Br)_2 \cdot HBr \longrightarrow HN(CH_2CH_2R)_2,$$

where R = $-SPO_3H_2$ (I), $-S_2O_3Na$ (II), $-SC(=NH_2)NH_2^+Br^-$ (III).

EXPERIMENTAL (CHEMISTRY)

Infrared spectra were obtained on a Bruker instrument. 2,2'-Dibromodiethylamine was obtained as described in [7], yield 41.7%, mp 198-199°C (literature mp 198-200°C).

Bis-(2-thiophosphatoethyl)amine (I). To a suspension of 4.46 g (25 mmole) of Na_3SPO_3 in 25 ml of water was added portionwise with vigorous stirring 3.9 g (12.5 mmole) of bis-(2-bromoethyl)amine. After a few minutes, 13 ml of dimethylformamide was added, and the re-

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TABLE 1. Toxicity and Radioprotectant Activity of (I) and (II)

Compound	LD_{50}, mg/kg	Dose, mg/kg	Survival %	P	MLA, days	S_{30}	Ip	α
I	825	200	30	$<0,05$	14,9	0,47	5,36	0,30
		400	30	$<0,05$	14,9	0,47	2,68	0,30
		530	65	$<0,05$	23,4	0,77	2,57	0,65
		—	0	—	11,0	0,33	—	—
II	1030	250	5	$>0,05$	13,5	0,42	4,12	0
		515	20	$>0,05$	17,3	0,55	2,32	0,16
		680	44	$<0,05$	21,5	0,70	2,14	0,41
		—	5	—	11,8	0,36	—	—

sulting solution kept at 20°C until a test for the SPO_3^{3-} ion was negative. The mixture was then treated with 200 ml of absolute ethanol, the mixture kept at −5°C for 24 h, and filtered. The solid was dried in vacuo over P_2O_5, then dissolved in 12 ml of glacial acetic acid, and precipitated with 100 ml of absolute ethanol. The product was purified by reprecipitation from water with ethanol, and dried in vacuo over P_2O_5 to give 3.40 g (73.7%) of product, mp 172-176°C. Found, %: C 12.92, H 5.28, N 3.27, S 17.68. $C_4H_{13}NO_6P_2S_2 \cdot 4H_2O$. Calculated, %: C 13.01, H 5.69, N 3.79, S 17.34. IR spectrum (KBr), cm^{-1}: $\nu_{P=O}$, 11.41, ν_{CH_2} 2934, 1449; δ_{NH} 1580; ν_{C-S} 725; ν_{P-S} 563.

Bis-(2-sodiothiosulfatoethyl)amine (II). 2,2'-Dibromodiethylamine hydrobromide (7.85 g; 25 mmole) was dissolved in 19 ml of water, and the solution heated to the boil. To the hot solution was added dropwise, gradually, a solution of 12.4 g (50 mmole) of $Na_2S_2O_3 \cdot 5H_2O$ in 22 ml (of water). The mixture was boiled for 1-2 h, then evaporated to half its volume. The product was repeatedly reprecipitated from water with ethanol, filtered, and dried in vacuo over P_2O_5, to give 6.50 g (87.5%) of product. Found, %: C 11.23, H 3.98, N 3.29, S 30.55, Na 10.69. $C_4H_9NNa_2O_6S_4 \cdot 4H_2O$. Calculated, %: C 11.62, H 4.12, N 3.39, S 30.99, Na 11.14. IR spectrum (KBr), cm^{-1}: $\nu_{S=O}$ 1215, 1045; ν_{C-S} 1024.

Bis-(2-isothiouronioethyl)amine Dibromide Hydrobromide (III). To a solution of 3.8 g (50 mmole) of thiourea in 35 ml of absolute ethanol was added 7.8 g (25 mmole) of 2,2'-dibromodiethylamine dihydrobromide. The solution was boiled for 3 h, cooled, and the solid which separated was filtered off, recrystallized from ethanol, and dried in vacuo over P_2O_5, to give 5.5 g (47.4%) of product. Found, %: C 15.3, H 4.23, N 14.94, S 13.66, Br 52.10. $C_6H_{15}N_5S_2 \cdot 3HBr$. Calculated, %: C 15.51, H 3.88, N 15.08, S 13.79, Br 51.70. IR spectrum (KBr), cm^{-1}: ν_{NH} 3302, 3174, 3080, 2767; $\nu_{C=NH}$ 1662, 1645, 1620; δ_{NH} 1531; ν_{C-S-C} 690.

EXPERIMENTAL (BIOLOGY)

The biological tests were carried out on male mice, strain ICR, weighing 20-25 g.

Acute toxicities (up to 72 h) were determined by the intraperitoneal route, the compounds being administered as solutions in distilled water. The hemilethal doses were determined by the method of Prozorovskii et al. [2].

Antiradiation activity was assessed by intraperitoneal administration of a range of doses (2/3, 1/2, and 1/4 of the LD_{50} values) of the test compounds in 0.5 ml of water to groups of 20 mice 15 min before irradiation with an absolute lethal dose of 9.0 Gy (^{137}Cs) in an IGUR-1 apparatus at a dose rate of 0.936 Gy/min. Survival was assessed daily up to 30 days. The data obtained were used to calculate the biometric criteria: mean lifespan of the animals which died (MLA), the Kaluszyner coefficient S_{30} [6], the protection coefficient α [4], and the protection index Ip [8].

The results are shown in Table 1. In view of its high toxicity (LD_{50} = 89 mg/kg), the radioprotectant activity of (III) was not examined. The results show that (I) has high protectant activity in doses of around 2/3 LD_{50}. The radioprotectant activity was lower at lower doses, but remained significantly greater than in the controls. Even in a dose of 200 mg/kg, protection remained significant, and the protection index high (Ip = 5.36), the compound possessing sufficient therapeutic breadth ($LD_{50}/ED > 4$). The radioprotectant properties of (II) were lower. A maximum effect of 44% survival with an MLA of 21.5 days was seen in the group receiving 680 mg/kg (2/3 LD_{50}). At the other doses tested, the increase in survival over the controls was not statistically significant, although there was a significant increase in lifespan.

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SYNTHESIS OF S-(2-AMINO-2-METHYLPROPYL)ISOTHIOUREAS AND THEIR RADIOPROTECTANT ACTIVITY

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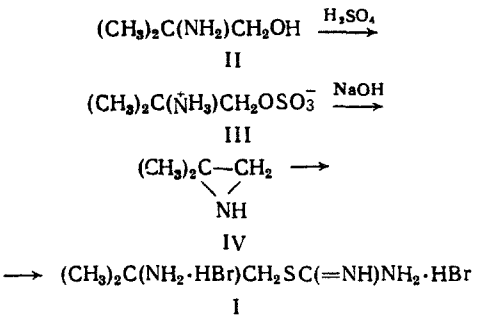
The most effective radioprotectant drugs include sulfur compounds such as mercaptoethylamine and mercaptopropylamine, and their derivatives, the corresponding S-aminoalkylisothioureas [5, 6]. It has been found experimentally that increasing the distance between the functional groups by more than three carbon atoms results in a decrease in antiradiation activity [5, 7]. This observation has led to an increased interest in aminoethyl- and aminoisopropylisothioureas.

We have previously found high radioprotectant activity in S-(2-aminopropyl)- and S-(1-amino-2-propyl)isothioureas [3]. S-(3-Aminobutyl)isothioureas show high antiradiation activity in mammals [2].

We now describe a method for the synthesis of S-(2-amino-2-methylpropyl)isothiourea dihydrobromide (I). The starting material used was 2-amino-2-methylpropan-1-ol (II), from which there was obtained 2-amino-2-methylpropyl sulfate (III), followed by 2,2-dimethylaziridine (IV). The desired compound (I) was obtained by reacting (III) with thiourea in dilute aqueous hydrobromic acid.



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