Therefore, the following conclusions can be drawn from the conducted study of the therapeutic action of solutions of PVP and methylpyrrolidone experimenting with animals with acute methanol intoxication. Firstly, all the investigated solutions of PVP give a detoxifying effect which increases somewhat with an increase of mol. wt. from 4500 to 46000. Secondly, it was observed that the solution with methylpyrrolidone does not show a detoxifying action and assists an increase in the toxic effect of methanol. Thirdly, in so far as methanol and its metabolites (formaldehyde and formic acid) do not interact with the PVP macromolecules in water, it is impossible to explain the mechanism of the observed effect of the polymers from the point of view of the possible complex formation of toxic substances of the indicated type with PVP.

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RADIOPROTECTIVE PROPERTIES OF 3-MERCAPTOINDOLE DERIVATIVES

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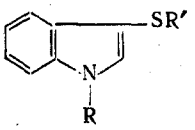
Among the heterocyclic compounds that may be promising radioprotectors, considerable attention is attracted by the indoles, containing various functional groups [6]. Investigations of the methods of synthesis and antitumor properties of indolylalkylamines led to the creation of the radioprotector preparation mexamine. A prophylatic effect of its closest analog, serotonin, is also known [4].

The introduction of a sulfhydryl group into the indole molecule permits a substantial expansion of the search for compounds possessing radioprotective properties. In connection with this, earlier we synthesized a series of substituted indoles based on 3-mercaptoindole (I) with various positions of the alkyl and vinyl groups at the nitrogen and sulfur heteroatoms (I-VIII) [2] and carried out the addition of EtSH at both vinyl groups of III with the formation of the trisulfide (IX) [3].

In this work the sulfides X-XII were produced by the addition of BuSH to vinyl indoles III, VII, and VIII.



I — XII

I: R = R′ = H; II: R = H, R′ = CH=CH$_2$; III: R = R′ = CH=CH$_2$; IV: R = H, R′ = Et; V: R = Et, R′ = H; VI: R = R′ = Et; VII: R = Et; R′ = CH = CH$_2$; VIII: R = CH = CH$_2$, R′ = Et; IX: R = R′ = (CH$_2$)$_2$SEt; X: R = R′ = (CH$_2$)$_2$SBu; XI: R = Et, R′ = (CH$_2$)$_2$SBu; XII: R = (CH$_2$)$_2$SBu, R′ = Et.

The addition of mercaptans to the thioindoles III, VII, adn VIII occurs under conditions of radical initiation at 80°C,. The alkylthioethylthioindoles IX-XII obtained are nonredistilling oily liquids, in view of which they were purified by column chromatography on Al_2O_3. The position of the vinyl group in compounds VII and VIII at different heteroatoms

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TABLE 1. Radioprotective Properties and Toxicity of 3-Mercaptoindole Derivatives

Compound	LD_{50}, mg/kg	Radioprotective effect		
		number of animals	dose, mg/kg	30-day survival, %
I	150	15	50	6
II	500	15	250	66
III	>1000	15	500	0
IV	>1000	10	500	10
V	150	10	50	0
VI	500	15	150	30,6
VII	>1000	15	300	0
IX	>1000	15	500	26
X	>1000	15	500	26
XI	>1000	15	500	6,6
XII	>1000	15	500	6
Control for irradiation	—	15	—	0

had no significnat effect on the reactivity of vinyl indoles in their interaction with mercaptans. In both cases monovinylthioindoles VII and VIII forms products with BuSH with high yields, reaching 90%.

In the thiylation of divinylindole III, replacement of the ethyl radical by the more voluminous butyl radical in the alkyl mercaptan leads to a decrease in the yield of the end product from 72 to 60%.

In the PMR spectra of compounds IX, X, and XII the signals of the protons of the NCH_2 group are characterized by a triplet (δ 4.16-4.20 ppm). The methylene protons bonded to the sulfur atom resonate in a stronger field (δ 2.25-2.33 and 2.63-2.76 ppm). The terminal methyl groups have signals at 0.80-1.39 ppm. The IR spectra of compounds of IX-XII do not have absorption at 1590 and 1640 cm^{-1}, due to the stretching vibrations of the vinyl groups at the sulfur and nitrogen atoms, respectively, and bands appear at 1380, 2870-2970 cm^{-1}, belonging to the stretching vibrations of the CH_2 and CH_3 groups.

EXPERIMENTAL CHEMICAL

The IR spectra were recorded on UR-20 instrument (German Democratic Republic) in a microlayer. The PMR spectra were obtained on a BS-487 spectrometer in CCl_4, internal standard HMDS. The purity and individuality of the starting materials and end products were monitored by thin-layer chromatography on Al_2O_3, solvent $CHCl_3$. The spots on the chromatogram were detected in iodine vapors.

3-Mercaptoindole (I) was synthesized by the method of [5]; alkyl- and vinyl indoles (II-VIII) were produced by the interaction of I with alkyl halides or with acetylene according to the procedure of [3].

1-[(2-Butylthio)ethyl]-3-[(butylthio)ethylthio]indole (X). A mixture of 2 mg (10 mmoles) of the thioindole III, 3.6 g (40 mmoles) BuSH and 0.02 g (1%) azoisobutyrodinitrile in a sealed ampul was exposed for 24 h at 80°C. The excess mercaptan was distilled off, the residue dissolved in $CHCl_3$ and purified on a column with Al_2O_3 (eluent $CHCl_3$). We isolated 2.2 g (60%) of the sulfide X, d_4^{20} 1.0895, n_D^{20} 1.5825. Found %: C 62.48; H 8.15; S 24.82. $C_{20}H_{31}NS_3$. Calculated %: C 62.94; H 8.19; S 25.20.

1-Ethyl-3[(2-butylthio)ethylthio]indole (XI) was produced by an analogous procedure. Yield 90%, d_4^{20} 1.0879, n_D^{20} 1.5894. Found %: C 65.43; H 7.84; S 21.45. $C_{16}H_{23}NS_2$. Calculated %: C 65.47; H 7.90; S 21.85.

1-[(2-Butylthio)ethyl]-3-(ethylthio)indole (XII) was produced analogously. Yield 90%, d_4^{20} 1.0875, n_D^{20} 1.5909. Found %: C 65.45; H 7.83; S 21.57. $C_{16}H_{23}NS_2$. Calculated %: C 65.47; H 7.90; S 21.85.

EXPERIMENTAL BIOLOGICAL

The investigations were conducted on C57BL/6 mice weighing 23-25 g. Irradiation was performed on an IGUR γ setup in a dose equal to LD_{95} (800 cGy) at a dose rate of 1.2 cGy/min. The substances were injected intraperitoneally 15 min before irradiation. All the tested compounds are insoluble in water; therefore they were introduced in the form of an aqueous emulsion with Tween-80 in a dose of 0.2 ml per mouse. The toxic doses of the substances were calculated by the method of Litchfield and Wilcoxon [1].

In a comparison of the toxicity of the compounds studied, it is noteworthy that the presence of an unsubstituted sulfhydryl group in compounds I-V is responsible for their high toxicity (LD_{50} 150 mg/kg). Substitution at both heteroatoms leads to a sharp decrease in the toxicity (LD_{50} 1000 mg/kg); an exception is diethylthioindole VI (LD_{50} 500 mg/kg).

A study of the radioprotective properties showed (see Table 1) that the greatest radioprotective activity is possessed by vinylthioindole II, which promotes the survival of 66% of the irradiated animals, while all of them die in the control experiments. Lower activity is possessed by diethylthioindole VI (30.6%). Variation of the length of the thioalkyl radical in the products of thiylation IX and X does not lead to any change in the radioprotective properties. For both compounds the survival rate is 26%, but this index is higher than in products XI and XII with one thiylated vinyl group (6.6 and 6%, respectively).

Thus, our investigations provide a basis for concluding that the search for radioprotective prepartions in a series of 3-mercaptoindole derivatives can be continued. The series of substituted 3-mercaptoindoles must be expanded to disclose the dependence of the radioprotective activity on their structure.

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