RADIOMODIFYING EFFICIENCY OF cis-2,6-DIPHENYLTETRAHYDROTHIOPYRAN-4-ONE DERIVATIVES

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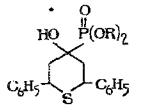
It is known that radioprotective compounds have been discovered in different classes of chemical compounds, in particular, among sulfur-containing compounds — aminothiols and their derivatives [5]. However, the wide use of aminothiols is limited because they cause side effects. This was the reason for synthesizing and studying the radiomodifying activity of cis-2,6-diphenyltetrahydrothiopyran-4-one derivatives.

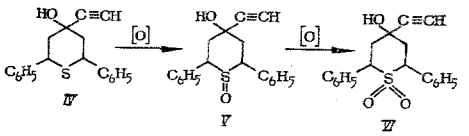
α-Hydroxyphosphonic esters [3] of the general formula were obtained by the Abramov reaction by reacting dialkyl phosphites with cis-diphenyltetrahydrothiopyran-4-one in the presence of a freshly prepared sodium alcoholate in the corresponding alcohol.



I-III

R = CH_3 (I), C_2H_5 (II), C_3H_7 (III)

The tertiary acetylenic alcohol (IV) was obtained by the Favorskii reaction [2] by nucleophilic condensation of acetylene with cis-2,6-diphenyltetrahydrothiopyran-4-one. Selective oxidation of this alcohol gave the corresponding sulfoxide (V) and sulfonic (VI) derivatives.



Compounds I-VI are colorless, high melting crystalline compounds, which are insoluble in water, but soluble in organic solvents. Their composition and structure was confirmed by the data of elemental analysis (Table 1) and IR spectroscopy. Foe compounds I-III absorption bands are observed in the 1215-1265 cm^{-1} region, corresponding to the stretching vibrations of the P=O group, at 1030-1040 cm^{-1} corresponding to the vibrations of the P—O—C group, and at 3250-3290 cm^{-1} corresponding to the OH group vibrations. In the IR spectra of compounds IV-VI there are absorption bands characteristic of the —C≡C— (2215-2230 cm^{-1}) and ≡C—H (3280 cm^{-1}) bonds, while in the IR spectrum of compound V there is a band of the S=O group (1020 cm^{-1}) and in that of compound VI, a band of the  group (1145-1310 cm^{-1}).

The compounds obtained were tested for radiomodifying activity during the action of X-rays in minimal absolutely lethal dose (MALD). The results were processes using the Fisher—Student criterion, and the differences were considered to be significant at the value of $P \leq 0.05$.

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TABLE 1. Phosphonic and Acetylenic Derivatives of Tetrahydrothiopyranol I-VI

Compound	Yield, %	Mp °C	Found, %				Empirical formula	Calculated, %			
			C	H	P	S		C	H	P	S
I	70	217-8	60,13	6,03	7,81	8,57	$C_{19}H_{23}O_4PS$	60,31	6,08	8,20	8,46
II	50	190-91	62,47	6,86	7,24	7,86	$C_{21}H_{27}O_4PS$	62,06	6,65	7,63	7,78
III	50	197-8	63,13	7,08	7,08	7,10	$C_{23}H_{31}O_4PS$	63,59	7,14	7,14	7,47
IV	80	134-5	77,30	6,92	—	10,77	$C_{19}H_{18}OS$	77,55	6,12	—	10,88
V	95	254-5	74,10	6,00	—	10,20	$C_{19}H_{18}O_2S$	73,54	5,80	—	10,32
VI	95	265-6	70,20	5,60	—	9,90	$C_{19}H_{18}O_3S$	69.93	5,52	—	9,81

TABLE 2. Toxicity and Radioprotective Activity of 2,6-Diphenyltetrahydrothiopyran-4-ol Derivatives I-VI

Compound	Type of animals	Number of animals	Irradiation dose, Gy	Toxicity LD_{50} /s, mg/kg	Dose, mg/kg	% survival
	Mice	20	8,0		Control	5,0
I	»	15	8,0	400,0	30.0	0
II	»	20	8,0	400,0	30.0	0
III	»	20	8,0	400,0	30,0	0
IV	»	20	8,0	400,0	30.0	0
IV	»	30	8,0	400,0	60.0	33,3
IV	»	30	8,0	400,0	120,0	8,3
V	»	30	8,0	400,0	60.0	40,0
VI	»	15	8,0	500,0	30.0	13,3
I, II	Rats	20 in each case	8,5	500,0	30.0	0
IV	»	20	8,5	500,0	30.0	10,0
V	»	20	8,5	500,0	30,0	20,0
	»	30	8,5		Control	0

EXPERIMENTAL (CHEMICAL) SECTION

cis-2,6-Diphenyl-4-dimethoxyphosphoryltetrahydrothiopyran-4-ol (I). A freshly prepared solution of sodium methylate in methanol is added dropwise to a mixture of 2.68 g (0.01 mole) of cis-2,6-diphenyltetrahydrothiopyran-4-one and 1.1 g (0.01 mole) of dimethyl phosphite, at such a rate that the temperature of the reaction mixture does not rise above 30-35°C. Sodium methylate is added until the reaction mixture no longer heats up. The colorless crystals are filtered, washed with water, dried, and washed with ether. The residue is recrystallized from alcohol. The yield is 2.64 g (70%) of compound I. Compounds II and III are obtained in a similar way in yields of 2.03 g (50%) and 2.17 g (50%), respectively.

2,6-Diphenyl-4-ethynyltetrahydrothiopyran-4-ol (IV). A 2000 ml portion of liquid ammonia and 16.8 g (0.3 mole) of powdered potassium hydroxide are placed in a three-necked flask fitted with a reflux condenser, dropping funnel, a stirrer, and a tube for passing the acetylene, and the mixture is saturated with acetylene with vigorous stirring for 2 h. Then, a solution of 40.2 g (0.15 mole) of 2,6-diphenyltetrahydrothiopyran-4-one in 550 ml of dry ether is added dropwise, with stirring, in the course of 2 h. At the end, the mixture is stirred for another 5 h while acetylene is vigorously passed in, and then allowed to stand overnight. The reaction mixture is then hydrolyzed by 120 ml of water, the ether solution is separated, and the aqueous solution is repeatedly extracted by ether. The combined ether extracts are neutralized by carbon dioxide and dried over potassium hydroxide. After removal of ether, 35.28 g (80%) of IV are obtained.

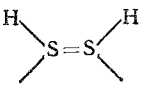
2,6-Diphenyl-4-ethynyltetrahydrothiopyran-4-ol 1-Oxide (V). A 5 ml portion of water is added to a solution of 2.94 g (0.01 mole) of carbinol (IV) in 60 ml of ether, and then, with vigorous stirring, a mixture of 1.2 ml of bromine and 0.5 ml of water is added. The carbinol–sulfoxide separates immediately in the form of a white precipitate. The preceipitate is filtered, washed with water, dried, and recrystallized from a 1:3 mixture of CCl_4 and $CHCl_3$. The yield of V is 284 g (95%).

2,6-Diphenyl-4-ethynyltetrahydrothiopyran-4-ol 1,1-dioxide (VI). Hydrogen peroxide (30%) is added, with stirring, to a mixture of 75 ml of acetic acid and 2.94 g (0.01 mole) of carbinol (IV) until the mixture becomes turbid. The mixture is left to stand for 3 days at room temperature. The crystals that separate are washed with water, filtered, and recrystallized from acetone. Yield, 3.10 g (95%) of VI.

EXPERIMENTAL (BIOLOGICAL)

The investigations were carried out on white nonpedigree mice, weighing 20-24 g each, an on male rats weighing 180 ± 5 g each. The irradiation was carried out on a RUM-17 apparatus under the following physicotechnical conditions: voltage 200 kV, current strength 15 mA, filter 3 mm Al (a 0.5 cm layer of Cu), dose rate, taking into account the back-scattering coefficient, 0.568 mA/kg. The irradiation doses of 8 and 8.5 Gy, were equal to $LD_{95/30}$ for the control animals. The compounds were administered 15 min before the irradiation perorally in a single dose in the form of a 1% solution of a 1:1:2 mixture consisting of DMSO, ethanol and physiological solution. The toxicity of the compounds studied was calculated by the method of probit analysis according to Leachfield and Wilkoxon [1]. The $LD_{50/3}$ for tetrahydrothiopyranone was 500 mg/kg on an average at $P = 0.05$. According to the accepted procedure of examination of the radiomodifying activity [4], the compounds were introduced in amounts of 1/2 and 1/8 of the $LD_{16/3}$ level, which is equal to 60 and 30 mg/kg, respectively. The radiomodifying activity was estimated by the survival criterion and destruction dynamics of the protected animals during 30 days of postirradiation period, according to the number of colony-forming cells of a spleen (CFU_S), and mean life time of dead animals.

The results of the investigation (Table 2) showed that of the compounds studied, cis-2,6-diphenyl-4-ethynyltetrahydrothiopyran-4-ol (IV) and its sulfoxide derivative cis-2,6-diphenyl-4-ethynyltetrahydrothiopyran-4-ol 1-oxide (V) have a pronounced radiomodifying action. The number of animals that survived in excess of those in the control with irradiation in a dose of 8.5 Gy was 10-20%, and increase in the mean life time was 2.1-2.3 days. When the mice were irradiated in a dose of 8 Gy, and the above compounds were introduced prophylactically, a 30-36% increase in the survival of the protected animals was discovered, compared with the control ($P < 0.05$). An increase in the CFU_S yield on the 8-9th day ($P = 0.01$) was also observed. Hence, these compounds can be considered to be radioprotective. It is possible that this action is based on mechanisms of the formation of a short-term mixed disulfide bond in the biopolymers of type:



It can be assumed that the radiomodifying activity of tetrahydrothiopyran derivatives is largely dependent on the functionally active groups in them and on the number of electron pairs on the sulfur hetero atom.

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