RESEARCH ON THE CHEMISTRY OF HETEROCYCLIC QUINONEIMINES.

2.* REACTION OF 3-PHENOTHIAZINONE WITH DIHYDRIC ALCOHOLS

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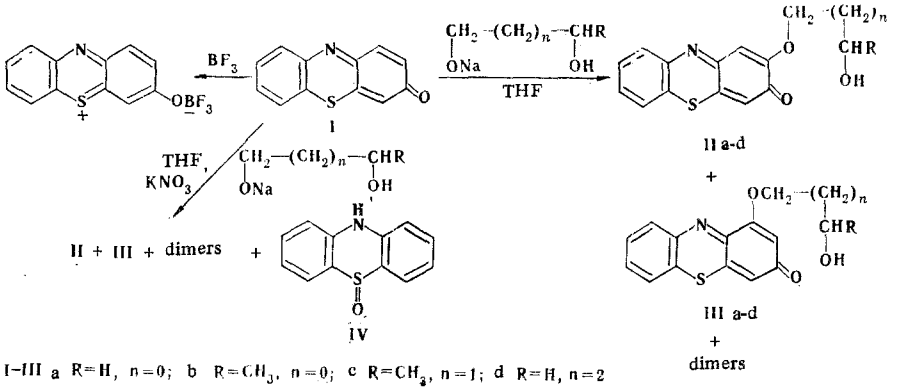
The reaction of 3-phenothiazinone with sodium salts of glycols, which leads to the formation of hydroxyalkoxy-3-phenothiazinones, was investigated. The presence of potassium nitrate as an oxidizing agent complicates the reaction by the formation of phenothiazine 5-oxide.

The possibility of the direct nucleophilic substitution of hydrogen in the 3-phenothiazinone molecule opens up prospects for the synthesis of new derivatives that may prove to be physiologically active compounds [2]. The increase in the membranotropicity of 3-phenothiazinone due to dihydric alcohol residues [3] may affect the spectrum of biological activity and other properties of the molecule.

We found that it was possible to introduce diol fragments into the 3-phenothiazinone molecule by using the monosodium salts of glycols as the nucleophilic agents. Primarily the 2-monosubstituted derivative (IIc) and a mixture of sodium salts of 3-phenothiazinone dimers are formed when a solution of 3-phenothiazinone (I) in tetrahydrofuran (THF) is refluxed with excess 1,3-butanediol monosodium salt. As in the reaction with alkoxides [1], the 1-monosubstituted derivative (IIIc) is formed in very small amounts. Traces of other products were detected by chromatography. The reaction proceeds similarly with ethylene glycol, 1,2-propanediol, and 1,4-butanediol (see the scheme presented below and Table 1).



I–III a R=H, n=0; b R=CH3, n=0; c R=CH3, n=1; d R=H, n=2

Nucleophilic substitution of hydrogen in 3-phenothiazinone evidently occurs only in the case of a primary hydroxy group. Like tert-butoxide, sodium 2,3-dimethylethyleneglycolate forms a complex mixture of products of self-condensation of 3-phenothiazinone upon reaction with the latter. The deep color of the reaction mixture and the presence of a signal in the EPR spectrum in the case of the reaction with sterically hindered anions constitute evidence in favor of a radical mechanism for the formation of self-condensation products.

Better yields were obtained in the reactions with glycolates when THF was used as the solvent. In excess amounts of the diols the reaction takes place only at temperatures close to their boiling points, and the yields of II and III are lower in this case. The reaction

*See [1] for communication 1.

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TABLE 1. Hydroxyalkoxy-3-phenothiazinones

Compound	mp, °C	Found, %				Empirical formula	Calc., %				R_f (ethyl acetate)	Yield, g/g of I
		C	H	N	S		C	H	N	S		
IIa	194—196	61,0	4,1	4,9	11,3	$C_{14}H_{11}NO_3S$	61,5	4,0	5,1	11,7	0,25	0,4
IIb	190—192	63,3	5,0	5,1	—	$C_{15}H_{13}NO_3S$	62,7	4,6	4,9	11,2	0,27	0,3
IIc	188—190	63,6	5,0	4,7	10,4	$C_{16}H_{15}NO_3S$	63,8	5,0	4,6	10,6	0,27	0,55
IId	138—140	63,5	5,0	4,9	10,7	$C_{16}H_{15}NO_3S$	63,8	5,0	4,6	10,6	0,3	0,45
IIIc	191—193	64,1	4,7	4,9	10,6	$C_{16}H_{15}NO_3S$	63,8	5,0	4,6	10,6	0,2	0,05

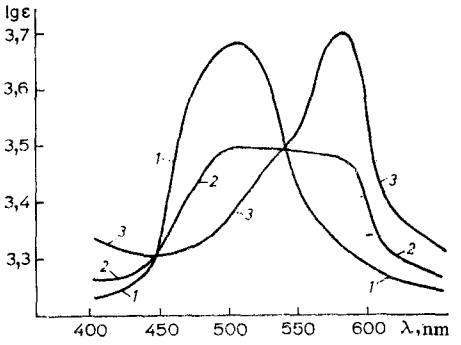

Fig. 1. Electronic absorption spectra of 3-phenothiazinone: 1) in ethanol; 2) in ethanol 1 h after the addition of boron trifluoride ethereate (V); 3) in ethanol 20 h after the addition of V.

temperature in the diols can be lowered significantly if a complex of the substrate with BF_3 is obtained beforehand. The significant bathochromic shift of the absorption maximum of 3-phenothiazinone in the visible region after mixing with BF_3 constitutes evidence for its formation. The existence of an isobestic point confirms the formation of a complex (Fig. 1).

The PMR spectra of the compounds contains two singlets at 6.9 and 7.0 ppm, which belong, respectively, to the 4-H and 1-H protons of the quinoneimine fragment of the molecule, a multiplet of aromatic protons at 7.5-8.3 ppm, and a signal of a hydroxy proton at 5.0 ppm. The PMR spectrum of III contains two doublets at 6.2 and 6.9 ppm with meta constant J = 15 Hz, which belong, respectively to the 4-H and 2-H protons of the quinoneimine fragment; this constitutes evidence that the substituent is in the 1 position of the 3-phenothiazinone molecule.

The characteristic frequencies of the absorption bands in the electronic and IR spectra of II and III do not differ from the frequencies observed for 2- and 1-monoalkoxy-3-phenothiazinones [1]. The absorption of the OH group in the IR spectra of II and III is recorded at 3350-3370 cm^{-1}.

The presence of an oxidizing agent [4], which creates conditions for removal of the "hydride" hydrogen, plays a substantial role in reactions involving nucleophilic substitution of hydrogen. A deficiency of an extraneous oxidizing agent in reactions with anionic nucleophiles leads to intensification of the formation of dimers due to oxidation of the intermediates by the starting 3-phenothiazinone. The use of potassium nitrate as the oxidizing agent led to an unexpected result. In addition to the usual reaction products, significant amounts of phenothiazine 5-oxide (IV), which was identified on the basis of the IR and PMR spectra, the results of elementary analysis, and a mixed-melting point determination with an authentic sample, were also isolated. The formation of the 5-oxide was not observed when other oxidizing agents (HgO, $CuCl_2$), as well as alcohols that do not give nucleophilic substitution products, were used. In the absence of a nucleophile potassium nitrate does not react with 3-phenothiazinone even under severe conditions.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Perkin—Elmer R-12B spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The

electronic spectra of solutions in ethanol were obtained with a Specord UV-vis spectrophotometer. The IR spectra of mineral oil suspensions were obtained with an IR-20 spectrometer. The purity of the compounds obtained was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates with ethyl acetate as the eluent.

Hydroxyalkoxy-3-phenothiazinones (IIa-d, IIIa-d). A) Sodium glycolate, obtained by dissolving 0.4 g (20 mmole) of sodium metal in 10 ml of the corresponding diol, was added with vigorous stirring to 2 g (10 mmole) of 3-phenothiazinone dissolved in 80 ml of tetrahydrofuran (THF) until the spot of the starting 3-phenothiazinone vanished on the thin-layer chromatogram. The THF was then removed by distillation, the residue was diluted with 100 ml of water, and products II and III were extracted with chloroform. The extract was dried and evaporated to a volume of 40-50 ml, and the concentrate was subjected to column chromatography on silica gel (40-100 μm) by elution with ethyl acetate. The red-orange fraction, which contained II, and the subsequent crimson fraction, which contained III, were collected. Removal of the eluent by distillation and crystallization of the residue from acetone gave II and III, the yields and constants of which are presented in Table 1.

B) A 2-g sample of potassium nitrate and sodium glycolate, obtained by dissolving 0.4 g of sodium metal in 10 ml of the corresponding diol, were added successively with vigorous stirring to a solution of 2 g (10 mmole) of 3-phenothiazinone in 80 ml of THF until the spot of the starting 3-phenothiazinone vanished on the thin-layer chromatogram. The subsequent isolation of the reaction products was realized by the method presented above. Colorless phenothiazine 5-oxide (IV) was also isolated from the eluate containing II. The mixture of II and IV was refluxed in 100 ml of acetone, during which II dissolved. The precipitated phenothiazine 5-oxide was removed by filtration and crystallized from ethanol to give 0.2-0.3 g of a colorless substance with mp 258-260°C. Found: C 66.8; H 4.2; N 6.6; S 15.0%. $C_{12}H_9NOS$. Calculated: C 66.95; H 4.2; N 6.5; S 14.9%. Compound IV was identical to the compound obtained by the method in [5].

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