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RESEARCH ON THE CHEMISTRY OF HETEROCYCLIC QUINONEIMINES.

REACTION OF 3-PHENOTHIAZINONE WITH ALKOXIDES

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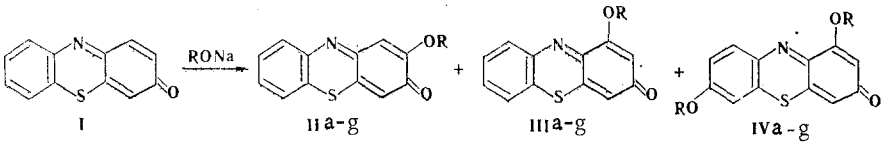
Nucleophilic substitution of hydrogen to give 1- and 2-mono- and 1,7-dialkoxy-3-phenothiazinones, as well as a mixture of dimers, when 3-phenothiazinone is treated with alkali metal alkoxides. The effect of the nature of the alcohol, the alkali metal cation, and the solvent on the reaction was investigated.

Very little study has been devoted to the reactions of quinoneimine systems with charged nucleophiles. In the present research we investigated the reaction of a heterocyclic quinoneimine, viz., 3-phenothiazinone, with alkali metal alkoxides, which is of particular interest in view of the great practical value of diphenazones [1].

It is known that quinones react with alcohols in the presence of Lewis acids under mild conditions to give products of nucleophilic substitution of hydrogen and dihydro compounds [2]. We have shown that 3-phenothiazinone does not react with alcohols even under activation (by means of H^+ and BF_3) conditions. However, nucleophilic substitution of hydrogen both in the quinoneimine and benzenoid fragments of the 3-phenothiazinone molecule to give three reaction products (II-IV), as well as a mixture of dimers (Scheme 1 and Table 1), occurs when solutions of 3-phenothiazinone in the corresponding primary alcohols are refluxed with the alkoxides.



I IIa-g IIIa-g IVa-g

II—IV a R=CH_3; b R=C_2H_5; c R=n-C_3H_7; d R=n-C_4H_9; e R=n-C_8H_{17}; f R=$CH_2C_6H_5$; g R=$CH_2CH{=}CH_2$

In the case of the reaction with sodium methoxide the IIa:IIIa:IVa product ratio is 9:4:1. The formation of only products of self-condensation was observed in the reaction of 3-phenothiazinone with sodium tert-butoxide; Farina and Valderrama [3] also were unable to obtain the tert-butoxy derivative from benzoquinone by means of nucleophilic substitution.

In addition to a multiplet of aromatic protons at 7.5-8.2 ppm and signals of protons of alkyl groups, two singlets at 6.9 and 7.1 ppm, which belong, respectively, to the 4H and 1H protons of the quinoneimine fragment of the molecule, are observed in the PMR spectra of products II; this indicates that the substituent enters the 2 position. In contrast to the PMR spectra of II, two doublets with spin-spin coupling constant (SSCC) J = 1.5 Hz are observed in the spectra of III. The signal of the 4H proton is found at 6.2 ppm in this case, i.e., it is shifted 0.7 ppm to strong field as compared with the signal of the 4H proton of II. The signal of the 2H proton is observed at 6.6 ppm. The observed differences in the PMR

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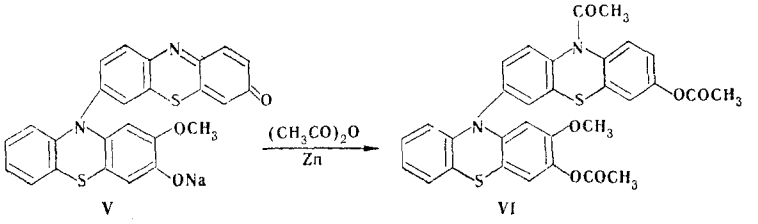
spectra of II and III are similar to those described for 1- and 2-alkoxy derivatives of 3-phenoxazinone [4]. Two doublets at 6.2 and 6.6 ppm, which are completely similar to the signals of the 4H and 2H protons of III (J = 1.5 Hz), are observed in the PMR spectra of IV; in addition, a well-resolved multiplet, which is characteristic for entry of the substituent in the 7 position of the aromatic part of the 3-phenothiazinone molecule, is found at 6.9-8.1 ppm. 1,7-Dimethoxyphenothiazinone, which is formed by direct nucleophilic substitution of hydrogen, is identical to the compound obtained by cyclization [5].

The electronic spectra of the alkoxy-3-phenothiazinones in the visible region contain an absorption maximum, the position of which depends on the position of the substituent in the quinoneimine fragment of the molecule. A hypsochromic shift of the absorption maximum in the visible region relative to unsubstituted 3-phenothiazinone to 505 nm is observed for the 2-alkoxy-3-phenothiazinones and for the 2-amino derivatives, whereas a bathochromic shift is observed for the 1-alkoxy- and 1,7-dialkoxy-3-phenothiazinones.

The IR spectra of the alkoxy-3-phenothiazinones contain characteristic (for quinoneimines) intense absorption bands at 1590-1630 cm^{-1}, which are due to interaction of the stretching vibrations of the C=C, C=O, and C=N bonds.

In addition to substitution products II-IV, dark-red, powdery, water-soluble compounds that contain sodium were always isolated in significant amounts for the reaction mixtures. The molecular mass of the compounds determined by conductometric titration (∿440) constitutes evidence for the presence of two phenothiazine fragments in their composition.* The reductive acylation of these products with acetic anhydride in the presence of powdered zinc gives a mixture of colorless acyl derivatives, from which we isolated, as the principal product, a compound, which, according to the results of elementary analysis, is a dimer that contains three acetyl groups and one methoxy group. The IR spectrum of the compound reveals the presence of an absorption band of a carbonyl group at 1694 cm^{-1} and a doubly more intense absorption band of a carbonyl group at 1778 cm^{-1}, which we assigned respectively, to the absorption of a carbonyl group bonded to the nitrogen atom of the phenothiazine fragment and to the absorption of two carbonyl groups that participate in ester bonds. In the IR spectrum of 3-acetoxy-10-acetylphenothiazine, which was used as a model compound, the absorption bands of the carbonyl groups have frequencies of 1675 and 1750 cm^{-1} vis-à-vis equal intensities. On the basis of literature analogies [6] the V structure may be likely for the sodium-containing dimer.



V VI

The formation of such dimers may take place through attack by the intermediately formed σ complex of starting 3-phenothiazinone to give stable sodium salt V, which in the presence of excess nucleophile is capable of undergoing further transformations involving the phenothiazinone fragment. The formation of dimers as a result of one-electron processes is also not excluded. The mixture evidently also contains dimers with a different mutual orientation of the fragments similar to those obtained by Diudea [7].

The ratio of the resulting alkoxy derivatives and self-condensation products depends to a considerable extent on the nature of the primary alcohol. The temperature of the onset of the reaction increases as the molecular mass of the alkoxide increases, and the reaction with n-butoxide takes place only when the corresponding alcohol is refluxed. An increase in the temperature of the onset of the reaction leads to a marked increase in the formation of the dimers, and the yield of alkoxy derivatives in the case of sodium octoxide is even less than 1% based on starting 3-phenothiazinone. The increase in the temperature of the onset of the reaction as the hydrocarbon part of the alcohol becomes larger is explained by the proportional decrease in its polarity and solvating capacity. Both polar and nonpolar aprotic solvents that are not capable of solvating alkali metal cations inhibit the reaction with alk-

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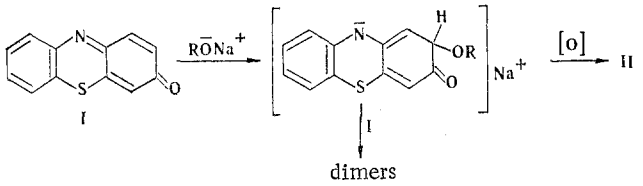
TABLE 1. Alkoxy-3-phenothiazinones

Compound	mp, °C	λ_{max}, nm	Found, %				Empirical formula	Calc., %				Yield (g/g of starting 3-phenothiazinone)	R^*_f
			C	H	N	S		C	H	N	S		
IIa	198—200	494	63,9	3,8	5,9	13,0	$C_{13}H_9NO_2S$	64,2	3,7	5,8	13,2	0,37	0,2
IIb	167—169	494	65,5	4,3	5,4	12,4	$C_{14}H_{11}NO_2S$	65,3	4,3	5,4	12,5	0,35	0,35
IIc	143—145	494	66,1	4,9	5,3		$C_{15}H_{13}NO_2S$	66,4	4,8	5,2	11,8	0,35	0,5
IId	105—107	494	67,7	5,4	4,6	11,0	$C_{16}H_{15}NO_2S$	67,3	5,3	4,9	11,2	0,32	0,6
IIe	88—90	494	70,3	7,0	4,1	8,9	$C_{20}H_{23}NO_2S$	70,3	6,8	4,1	9,4	0,3	0,8
IIf	186—188	494	71,3	4,2	4,3	9,9	$C_{19}H_{13}NO_2S$	71,4	4,1	4,4	10,0	0,4	0,65
IIg	140—142	494	67,0	4,1	5,4		$C_{15}H_{11}NO_2S$	66,9	4,4	5,2	11,9	0,32	0,52
IIIa	225—227	509	64,2	3,9	6,2	12,9	$C_{13}H_9NO_2S$	64,2	3,7	5,8	13,2	0,16	0,15
IIIb	197—199	509	61,1	4,8	5,1	11,5	$C_{14}H_{11}NO_2S \cdot H_2O$	61,1	4,8	5,1	11,6	0,15	0,2
IIId	122—124	509	67,4	5,5	4,8	11,1	$C_{16}H_{15}NO_2S$	67,3	5,3	4,9	11,2	0,1	0,35
IVa	251—253	510	61,0	4,2		11,6	$C_{14}H_{11}NO_3S$	61,5	4,0	5,1	11,7	0,04	0,05
IVb	177—179	510	63,5	5,0	5,0		$C_{16}H_{15}NO_3S$	63,7	5,1	4,6	10,6	0,03	0,07

oxides virtually completely. The use of tetrahydrofuran (THF), which effectively solvates alkali metal cations [8], as the reaction medium made it possible to decrease the temperature of the reactions with the alkoxides of high-boiling solvents to the boiling point of THF (65°C). In strongly polar aprotic solvents [dimethyl sulfoxide (DMSO) and dimethylformamide (DMF)] alkoxides evidently reduce 3-phenothiazinone, like 3-phenoxazinone [9, 10], to an anion radical, which leads to considerable complication of the reactions due to radical processes. The formation of alkoxy derivatives is not observed in this case. The nature of the alkali metal cation (Li^+, Na^+, and K^+) has virtually no effect on the course of the reaction of 3-phenothiazinone with alkoxides.

Depending on the reaction conditions, air oxygen, as well as the substrate itself, may serve as the agent for oxidation of the resulting σ complexes, i.e., the oxidation methods that are normal for quinones are realized in the case of 3-phenothiazinone. A sufficient amount of an external oxidizing agent (air) facilitates rapid reactions accompanied by minimal formation of self-condensation products. In an argon atmosphere the yields of alkoxy derivatives decreases significantly due to the formation of dimers, since the oxidizing agent in this case is the starting 3-phenothiazinone.



In the case of the reaction with alkoxides we have observed for the first time substitution of the hydrogen atom in the 1 position of the 3-phenothiazinone molecule, whereas the formation of 2- and 7-mono- and 2,7-disubstituted derivatives was previously established in the reaction of 3-phenothiazinone with amines [11].

The reaction with alkoxides opens up a pathway to new 3-phenothiazinone derivatives that are difficult to obtain when other synthetic methods are used.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in chloroform or d_6-DMSO were recorded with a Perkin—Elmer R-12B spectrometer 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 recorded with a UR-20 spectrometer. The purity of the compounds obtained was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates by elution with benzene—ethyl acetate (1:1).

Alkoxy-3-phenothiazinones IIa-c, IIIa-c, and IVa-c. The sodium alkoxide, which was obtained beforehand by dissolving 0.1 g (5 mmole) of sodium metal in 10 ml of the corresponding alcohol, was added with stirring to a solution of 1 g (5 mmole) of 3-phenothiazinone in 50 ml of the same alcohol, and the mixture was refluxed until the spot of the starting 3-phenothiazinone vanished on the chromatogram. The reaction mixture was then poured into 300 ml of

water, and the precipitated alkoxy derivatives of 3-phenothiazinone were removed by filtration, dried, and dissolved in 25 ml of chloroform. The chloroform solution was chromatographed with a column filled with silica gel (40-100 μ), and three zones, viz., orange, red-violet, and brown zones, were collected successively. Removal of the eluent from these fractions by distillation gave, respectively, 2- and 1-mono- and 1,7-dialkoxy-3-phenothiazinones.

Alkoxy-3-phenothiazinones IId-g. These compounds were similarly obtained using THF as the solvent instead of the corresponding alcohols. At the end of the reaction (as determined by disappearance of quinone I on the chromatogram) the THF was removed by distillation, and the alkoxy derivatives were extracted from the resulting precipitate by means of chloroform. The subsequent separation was accomplished by the method described above.

All of the alkoxy-3-phenothiazinones were crystallized from acetone. The characteristics of the alkoxy-3-phenothiazinones are presented in Table 1. Compounds IIId-g and IVd-g were identified only by means of TLC.

Determination of the Molecular Mass of the Self-Condensation Products. The mixture of water-soluble products, which was purified beforehand by extraction with chloroform to remove the admixed alkoxy derivatives of 3-phenothiazinone, was titrated with 1 N HCl to record the conductometric titration curve. For this, a weighed 0.1955-g sample of the mixture of products was dissolved in 90 ml of distilled water, and the solution was subjected to conductometric titration. The molecular mass was determined from the formula $M = g/vN \cdot 0.001$, where g is the weight of the investigated substance in grams, v is the volume of acid consumed in titration in milliliters, and N is the normality of the acid.

The volume of the acid consumed in the titration was determined from the inflection point of the titration curve. In this case 0.4 ml of acid was consumed in the titration, and this gives $M = 0.1955/04 \times 1.115 \times 0.001 = 438$, which corresponds to the molecular mass of a dimer containing one sodium atom and one methoxy group. Found: M 438. $C_{25}H_{15}N_2O_3S_2$. Calculated: M 446.54.

Reductive Acylation of the Mixture of Dimers. A 1-g sample of the mixture of sodium-containing dimers was refluxed for 30 min in 50 ml of acetic anhydride in the presence of 2 g of powdered zinc, during which the color of the solution changed from dark red to yellow-brown. The zinc was removed by filtration, and the filtrate was added with stirring to 300 ml of cold water. The resulting precipitate was removed by filtration, dried, and dissolved in benzene, from which 0.2 g of a yellowish product, the elementary composition of which corresponded to the empirical formula of dimer VI, was precipitated by the addition of ether. IR spectrum: 1695 (C=O) and 1778 cm^{-1} (C=O). Found: C 63.7; H 4.1; N 4.8; S 11.0%. $C_{31}H_{24}N_2O_6S_2$. Calculated: C 63.6; H 4.1; N 5.2; S 10.7%.

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