perature was 130°C, the ionizing voltages were 75 and 15 eV, and the emission current was 250 μA.

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RESEARCH IN THE CHEMISTRY OF HETEROCYCLIC QUINONEIMINES.

5.* EFFECT OF BENZANNELATION OF PHENOTHIAZIN-3-ONE ON ITS REACTION WITH O- AND S-NUCLEOPHILES

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Benzo[a]phenothiazin-5-one reacts with alkoxides, thiols, or thiolates to give 6-alkoxy- and 6-alkyl(aryl)thiobenzo[a]phenothiazin-5-ones, respectively. Benzannelation of phenothiazin-3-one in the quinoneimine fragment markedly hinders reactions with O- and S-nucleophiles with retention of the reaction center in the quinoneimine fragment of the molecule.

The areas of application found for a number of benzo[a]phenothiazin-5-one derivatives (laser technology [2], color photography [3], and pharmacological activity [4]) have stimulated the search for methods for the synthesis of compounds of this series [3, 5, 6]. A number of new studies [6, 7] have been devoted to the direct introduction of substituents into benzo[a]phenothiazin-5-one by its reaction with radical agents under conditions of chemical and photochemical generation. It seemed of promise to study the direct nucleophilic substitution of hydrogen in benzo[s]phenothiazin-5-one, since the latter is easy to prepare, and reactions of this sort have been unknown for it up until now.

Benzannelation in the quinoneimine fragment in the case of phenoxazin-3-one markedly decreases its reactivity with respect to nucleophiles; however, under conditions of activation of the substrate with mineral acid p-thiocresol reacts with benzo[a]phenoxazin-5-one to give a product of substitution in the aryl fragment of the molecule [8].

In contrast to phenothiazin-3-one [1, 9], the reactions of benzo[a]phenothiazin-5-one with both thiols and thiolates and alkoxides are also markedly hindered as a result of blocking of the most electrophilic centers of the molecule by benzannelation. The most essential condition for the reactions with all of the three examined series of nucleophiles is the polarity of the solvent. The reactions do not occur in benzene and tetrahydrofuran (THF); good results are obtained when the reactions are carried out in dimethylformamide (DMF) at ∿100°C.

*See [1] for Communication 4.

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Under the indicated conditions benzo[a]phenothiazin-5-one (I) reacts with thiols under conditions of prior activation by mineral acids. 6-Alkyl(aryl)thiobenzo[a]phenothiazin-5-ones (II) are formed as the only substitution products; however, a considerable amount of I is converted to the colorless dihydro form, viz., 5-hydroxybenzo[a]phenothiazine, which, in contrast to 3-hydroxyphenothiazine, is oxidized only slowly in air. To increase the degree of conversion of benzo[a]phenothiazin-5-one to the 6-substituted derivatives, the process must be carried out repeatedly with regeneration of the starting compound from the dihydro form by bubbling air into the reaction mass.

The reaction of I with thiolates proceeds considerably faster than the reaction with thiols both due to an increase in the nucleophilicity of the reagent and to the greater ease of oxidation in air of the 5-hydroxybenzo[a]phenothiazine anion. Anionic activation of the reagent, instead of the cationic activation of the substrate that is used in the reaction with thiols, does not affect the regioselectivity of the process in this case. Benzo[a]-phenothiazin-5-one gives exclusively 6-alkyl(aryl)thiobenzo[a]phenothiazin-5-ones with thiols in both ethanol and DMF, whereas benzo[a]phenoxazinone forms 9-tolylbenzo[a]phenoxazin-5-one with thiocresol in ethanol [8]. 6-Substituted derivatives were also the only products in the case of radical substitution of hydrogen in benzo[a]phenothiazin-5-one and benzo[a]phenoxazin-5-one by thiols [6].

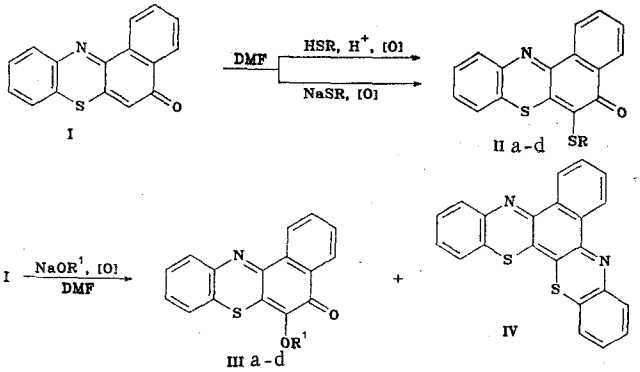
In contrast to the reaction of phenothiazin-3-one [9], the reaction of benzo[a]phenothiazin-5-one with alkoxides is not accompanied by the formation of self-condensation products; however, severe conditions lead to the accumulation in the reaction mixtures of very small amounts of a deeply colored compound, viz., benzo[a][1,4]benzothiazino[3,2-c]phenothiazine (IV), which was identified on the basis of microanalytical data and by comparison with a sample obtained by the method in [10]. The formation of IV in addition to 6-alkoxybenzo[a]phenothiazin-5-ones (III) constitutes evidence for partial destruction of benzo[a]-phenothiazin-5-one to give an o-aminothiophenol fragment, which immediately condensed with the substrate to give IV; this was confirmed experimentally — the condensation of o-aminothiophenol with benzo[a]phenothiazin-5-one in DMF gives a product identical to IV.

The reaction of benzo[a]phenothiazin-5-one with the monosodium salt of 1,4-butanediol is similar to the reaction with alkoxides. Upon the whole, alkoxides are less reactive with respect to I than thiols and thiolates.

The structures of II and III were established unambiguously by means of PMR spectroscopy from the disappearance of the singlet of the 6-H proton in the spectra of the substituted compounds at 7.0 ppm, in agreement with the data obtained by Ueno and co-workers [6]. As in the PMR spectrum of unsubstituted benzo[a]phenothiazin-5-one, four groups of complex multiplets of protons of aromatic fragments of the molecule, which undergo a small strong-field shift in the case of the tolylthio-substituted compound, are present in the PMR spectra of II and III.

A bathochromic shift of the absorption maximum relative to unsubstituted benzo[a]-phenothiazin-5-one (λ_{max} = 480 nm) is observed in the spectra in the visible region of II and III.

The IR spectra of derivatives II and III contain intense absorption bands of a quinoneimine fragment at 1590-1630 cm^{-1}. The absorption of the hydroxy groups in IId and IIIe is recorded at 3450 cm^{-1}.



a, $R^1=CH_3$; b, $R^1=C_2H_5$; c, $R^1=C_4H_9$; d, $R^1=(CH_2)_4OH$

TABLE 1. 6-Alkyl(aryl)thiobenzo[a]phenothiazin-5-ones (II) and 6-Alkoxybenzo[a]phenothiazin-5-ones (III)

Compound	mp, °C	λ_{max}, nm	R_f (chloroform)	Found, %				Empirical formula	Calc., %				Yield, g/g of I
				C	H	N	S		C	H	N	S	
IIa	176—178	508	0,35	67,4	4,6	4,0	18,9	$C_{19}H_{15}NOS_2$	67,2	4,5	4,1	19,0	0,4—0,6
IIb	60—62	508	0,4	70,5	6,3	3,3	15,4	$C_{24}H_{25}NOS_2$	70,7	6,2	3,4	15,7	0,4—0,6
IIc	184—186	508	0,45	71,4	4,0	3,5	16,3	$C_{23}H_{15}NOS_2$	71,7	3,9	3,6	16,6	0,4—0,6
IId	172—174	508	0,1	63,4	3,9	4,0	19,2	$C_{18}H_{13}NO_2S_2$	63,6	3,9	4,1	18,9	0,4—0,6
IIIa	178—180	503	0,7	69,7	3,9	5,0	10,9	$C_{17}H_{11}NO_2S$	69,4	4,1	4,8	10,9	0,4—0,6
IIIb	150—152	503	0,75	70,5	4,2	4,5	10,3	$C_{18}H_{13}NO_2S$	70,3	4,2	4,5	10,4	0,4—0,6
IIIc	76—78	503	0,8	71,6	5,2	4,2	9,4	$C_{20}H_{17}NO_2S$	71,6	5,1	4,2	9,6	0,4—0,6
IIId	98—99	503	0,1	68,2	4,9	4,2	9,0	$C_{20}H_{17}NO_3S$	68,3	4,9	4,0	9,1	0,4—0,6

Thus a significant effect of annelation in the quinoneimine fragment, which leads to a decrease in the electrophilicity of the molecule, is apparent in the examined reactions of benzo[a]phenothiazin-5-one with nucleophiles. The result is an increase in the energy barrier of the reaction and an increase in the regioselectivity of substitution with retention of the electrophilic center in the quinoneimine fragment of the molecule.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in chloroform 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 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 chloroform.

6-Alkyl(aryl)thiobenzo[a]phenothiazin-5-ones (IIa-d). A) Reaction of benzo[a]phenothiazin-5-one with thiols. A solution of 0.5 g (2 mmole) of I in 50 ml of DMF was heated to 100°C, two to three drops of concentrated HCl were added, and a fivefold excess (with respect to the equimolar value) of the thiol was added all at once with vigorous stirring. The reaction mixture became colorless briefly, after which it was stirred for another hour. The addition of the thiol and acid can then be repeated. After standing for an additional 2-3 h, the reaction mixture was treated with 100 ml of water, and the resulting precipitate was removed by means of fluted filter paper. The precipitate was dried, dissolved in the minimum amount of chloroform, and chromatographed on silica gel (100-250 μ) by elution with chloroform. The first (brown) fraction, which contained product II, and the second (red) fraction, which contained unchanged I, were collected. Removal of the eluent by distillation gave, depending on the type of thiol, up to 0.3 g of II and up to 0.3 g of starting compound. 6-Alkyl(aryl)thio-substitued II were crystallized from acetone. The characteristics of the compounds are presented in Table 1.

B) The reaction of benzo[a]phenothiazin-5-one with thiolates was carried out under the same conditions as in the reaction with thiols but without the addition of a mineral acid. It was also necessary to use a large (fivefold to tenfold) excess of the alkoxide and to carry out the reaction repeatedly. The total time of the process may be substantially shorter than in the reaction with thiols. The products were isolated and purified as in method A. The yields of the compounds were the same as in method A.

6-Alkoxybenzo[a]phenothiazin-5-ones (IIIa-e). Benzo[a][1,4]benzothiazino[3,2-c]phenothiazine (IV) (Method A). A solution of 0.5 g (2 mmole) of I in 50 ml of DMF was heated to 100°C, and a tenfold to 15-fold excess of the alkoxide was added to it with vigorous stirring. The reaction was carried out under these conditions for 12-16 h with monitoring of the formation of the substitution product by means of TLC. The mixture was then cooled and diluted with 100 ml of water, and the precipitate was removed by filtration through a fluted filter paper. The precipitate was dried, dissolved in the minimum amount of chloroform, and chromatographed with a column packed with silica gel (100-250 μ) by elution with chloroform. The first (violet) zone, which contained IV, the second (red-brown) zone, which contained III, and the third (red) zone, which contained starting benzo[a]phenothiazin-5-one, were collected. Removal of the eluent by distillation gave up to 0.3 g of products III, up to 0.3 g of starting compound, and up to 0.01 g of IV. The yield of IV can be increased substantially by carrying out the reaction with alkoxides under more severe con-

ditions. The 6-alkoxybenzo[a]phenothiazin-5-ones were crystallized from acetone. The characteristics of the compounds are presented in Table 1. Compound IV was also obtained from 2,3-dichloronaphthoquinone and o-aminothiophenol by the method in [10] (method B).

Benzo[a][1,4]benzothiazino[3,2-c]phenothiazine (IV) (Method C). A solution of 0.25 g (1 mmole) of I in 25 ml of DMF was heated to 100°C, and 0.13 g (1 mmole) of o-aminothiophenol was added to it with stirring. After stirring for 1 h, the reaction mixture was diluted with 50 ml of water, and the resulting precipitate was removed by filtration, dried, dissolved in 25 ml of chloroform, and chromatographed with a column packed with silica gel (100-250 μ) by elution with chloroform. The first (violet) fraction was collected, and the eluent was removed to give 0.14 g (40%) of IV in the form of violet crystals with mp 290°C (mp 291°C [10]) and R_f 0.95 (chloroform). Found: C 71.7; H 3.7; N 117.4%. $C_{22}H_{12}N_2S_2$. Calculated %: C 71.7; H 3.7; N 117.6%. No melting-point depression was observed for mixtures of IV obtained by the methods described above.

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SYNTHESIS OF 1,3,4-TRIPHENYL-1H-PYRAZOLO[3,4-e][1,4]THIAZEPIN-7-ONE

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The reaction of 5-amino-1,3-diphenylpyrazole with benzaldehyde gives 5-benzylideneamino-1,3-diphenylpyrazole, which then undergoes cyclization with mercaptoacetic acid to give 1,3,4-triphenyl-1H-pyrazolo[3,4-e][1,4]thiazepin-7-one.

The available data relative to the synthesis of pyrazolothiazepines by the reaction of 5-aminopyrazoles with benzaldehyde and mercaptoacetic acid are contradictory. Reactions involving the formation of 5-benzylideneaminopyrazoles II and their subsequent cyclization to pyrazolo[3,4-d][1,3]thiazepines IV [1], as well as reactions with the isolation of intermediate 4-benzylidene-5-iminopyrazoles III, which subsequently react with mercaptoacetic acid to give pyrazolo[3,4-e][1,4]thiazepines V [2-5], have been described.

However, repetition of the syntheses in the case of 5-amino-1,3-diphenylpyrazole (I) in order to obtain isomeric pyrazolothiazepines IV and V led us to the conclusion that only 5-benzylideneamino-1,3-diphenylpyrazole (II) is an intermediate [which was proved by hydrogenation of the latter with sodium borohydride to 5-benzylamino-1,3-diphenylpyrazole (VI)], and only one pyrazolothiazepine is also formed. Pyrazolothiazepine V was subjected

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