COMPARATIVE STUDY OF REACTION OF 3-PHENOTHIAZINONE, 5-ETHYL-3-PHENAZINONE, AND 5-PHENYL-3-PHENAZINONE WITH p-THIOCRESOL

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The reactivity of the 7 position in 3-phenothiazinone, 3-phenoxazinone, and 5-ethyl- and 5-phenylphenazinone in reactions with p-thiocresol is determined by the nature of the two heterobridges, which can be arranged in the order S, O, N–C_2H_5, N–C_6H_5 with respect to decreasing electrophilicity of this position.

We have previously established that 3-phenothiazinone (I) [1] reacts with amines that have high nucleophilicity to give products of monosubstitution at the 2 position of the quinoid ring or the 7 position of the benzenoid ring. Under similar conditions 3-phenoxazinone (II) [2] undergoes reaction only at the quinoid ring. The reactions of 5-ethyl- (III) [3] and 5-phenyl-3-phenazinones (IV) [4] proceed with greater difficulty than in the case of the oxygen-containing analog (II), and a phenyl substituent attached to the nitrogen atom hinders substitution to a great degree. At the same time, it is known that 3-phenoxazinone reacts with p-thiocresol in alcohol at room temperature to give isomeric products of monosubstitution at the 2 or 7 position, as well as a 2,7-disubstituted compound [5]. It might have been expected that the reactivity of the benzenoid ring would be manifested in the case of other heterocyclic quinones (I, III, and IV) with a stronger nucleophile.

To ascertain the effect of the nature of a second heterobridge (S, O, N–C_2H_5, and N–C_6H_5) on the reactivity of the benzenoid ring we made a comparative study of the reaction of p-thiocresol with the heterocyclic quinones cited above.

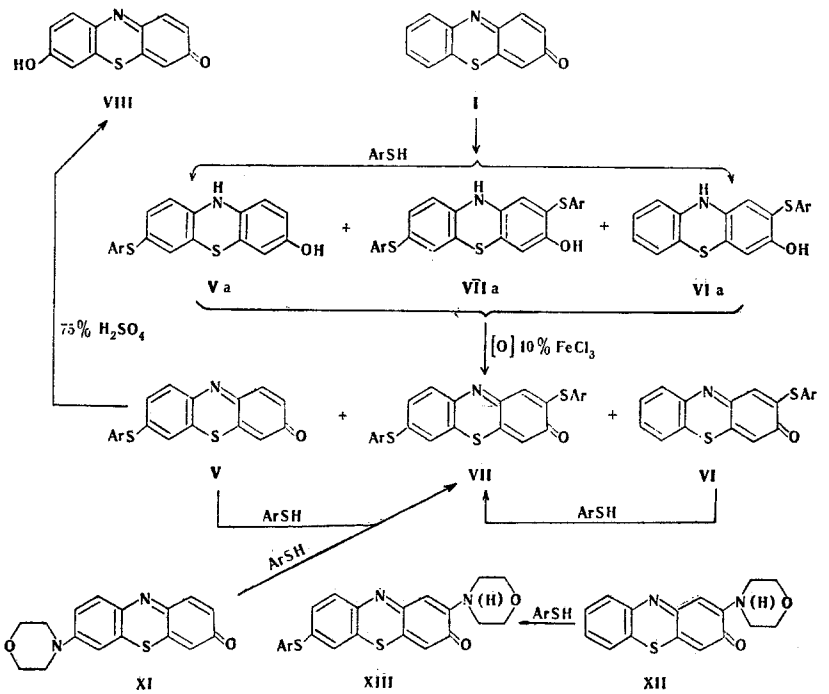

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TABLE 1. p-Tolylthio Derivatives of 3-Phenothiazinone, 5-Ethyl-3-phenazinone, and 5-Phenyl-3-phenazinone

Compound	mp, °C	Found, %				Empirical formula	Calc., %				Visible spectrum			R_f	Yield, %
		C	H	N	S		C	H	N	S	λ_{max}, nm	$\Delta\lambda_{max}$, nm	lg ε		
V	165—166[b]	68,4	4,0	4,2	18,6	$C_{19}H_{13}NOS_2$	68,5	3,9	4,2	19,1	244 373 523	−18	4,38 3,92 3,68	0,29	21
VI	253—256[b]	68,2	4,0	4,4	18,6	$C_{19}H_{13}NOS_2$	68,5	3,9	4,2	19,1	265 457	+48	4,52 4,26	0,59	27
VII	208—210[c]	67,9	4,2	3,6	21,1	$C_{26}H_{19}NOS_3$	68,2	4,1	3,1	21,1	261 465	+42	3,92	0,73	20
XIV	125—126[b]	65,6	4,8	6,7	15,3	$C_{28}H_{26}N_2O_2S_2$	65,7	4,8	6,8	15,2	264 491	+14	4,76 4,19	0,58	65
XV	260—261[b]	72,3	5,3	7,8	9,2	$C_{21}H_{18}N_2OS$	72,8	5,2	8,1	9,2	236 429 510	+14	3,50 3,32 3,05	0,60	20
XVI	226—227[d]	71,0	5,1	6,0	13,8	$C_{28}H_{24}N_2OS_2$	71,7	5,2	6,0	13,8	318 461 516	+9	3,48 3,41 3,31	0,51	26
XVIII	265—267[c]	75,6	4,5	7,1	8,0	$C_{25}H_{21}N_2OS$	76,0	5,6	7,1	8,1	452 519	+15	3,27 2,96	0,70	20

[a]In DMF. [b]From butanol. [c]From butyl alcohol—ethanol (1:2). [d]From benzene—ethyl acetate (1:2).

In fact, the reaction of 3-phenothiazinone with p-thiocresol proceeds readily in alcohol when catalytic amounts of hydrochloric acid are either present or absent and faster than in the case of 3-phenoxazinone [5]; the formation of colorless 3-hydroxyphenothiazine derivatives (Va-VIIIa) (after 1 and 4 h, respectively) is observed under similar conditions.* In addition, the resulting 3-hydroxy derivatives of phenothiazine are converted to the oxo derivatives, in contrast to the 3-hydroxy derivatives, only under the influence of an oxidizing agent (for example, a 10% solution of ferric chloride). Two monosubstituted derivatives of 3-phenothiazinone (V and VI) and one containing two p-thiocresol residues (VII) were isolated from the reaction mixture, after oxidation, by column chromatography on silica gel (Table 1).

The presence of a substituent in the 2 position in VI, which is characterized by a hypsochromic shift of the long-wave band in the electronic spectrum relative to unsubstituted 3-phenothiazinone ($\Delta\lambda$ 48 nm), was confirmed by the absence of a signal of a 2-H proton in the PMR spectrum at 6.83 ppm as compared with the spectrum of unsubstituted 3-phenothiazinone: 1-H δ 7.58 ppm; 2-H δ 6.83 ppm; 4-H δ 6.74 ppm.

Conversion to the previously described 7-hydroxy-3-phenothiazinone (VIII) [6] by hydrolysis with 75% sulfuric acid serves as proof for the incorporation of a p-thiocresol residue in the 7 position in V. The formation of bis(p-tolythio)-3-phenothiazinone identical to VII when monosubstituted V and VI are treated with p-thiocresol serves as confirmation of the fact that VII contains two p-tolylthio residues in the 2 and 7 positions.

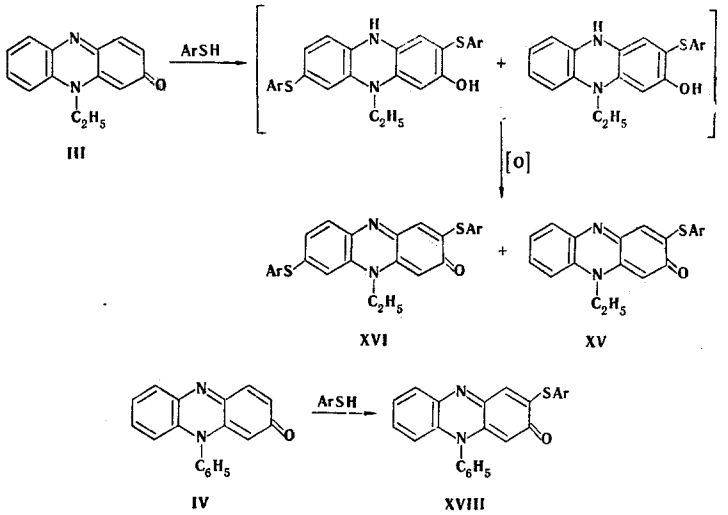
The increased reactivity of the 7 position of the benzenoid ring of 3-phenothiazinone as compared with 3-phenoxazinone is evidenced not only by the high yields of 7-monosubstituted compounds (20 and 10% [5], respectively) but also by the ease of displacement of the substituent in this position. Thus whereas the ethoxy group is not displaced and 2-(p-tolylthio)-7-ethoxy-3-phenoxazinone (X) is formed when 7-ethoxy-3-phenoxazinone (IX) is refluxed with p-thiocresol in alcohol, under similar conditions 7-morpholino-3-phenothiazinone (XI) is converted completely to 2,7-bis(p-tolylthio)-3-phenothiazinone (VII). The hydrogen atom in the benzene ring of 2-morpholino-3-phenothiazinone (VII) is also replaced more readily than in the case of the corresponding 3-phenoxazinone derivative [2]; however, in contrast to the latter, XII is converted to 2-morpholino-7-(p-tolylthio)-3-phenothiazinone.

The use of a stronger nucleophile (p-thiocresol) in the case of 5-ethyl-3-phenazinone led, in contrast to the reactions with amines, to the formation of two reaction products: 2-(p-tolylthio)- (XV) and 2,7-bis(p-tolylthio)-5-ethyl-3-phenazinone (XVI). The yields of XV and XVI in alcohol were low (7-10%). As in the case of 3-

* The reactions were carried out in alcohol at room temperature with an identical molar ratio of the starting reagents.

phenothiazinone and 3-phenoxazinone, the reaction proceeds through a step involving the formation of colorless 3-hydroxy derivatives of 5-ethylphenazine, but their formation was accomplished only after standing at room temperature for 6 h. In the case of oxidation with air oxygen the reaction mixture immediately turns reddish-brown, which indicates the lower stability of hydroxy derivatives of 5-ethylphenazine.

In contrast to the reaction with the corresponding 3-phenoxazinone derivative [5], only the amine residue in the 2 position is replaced in the reaction of a twofold excess of p-thiocresol with 2-morpholino-5-ethyl-3-phenazinone (XVII). 2,7-Bis(p-tolylthio)-5-ethyl-3-phenazinone (XVI) can be obtained only when a fourfold excess of p-thiocresol is used. The hindered formation of 2,7-disubstituted 5-ethyl-3-phenazinone both by direct reaction of 5-ethyl-3-phenazinone and from its 2-morpholino derivative (XVII) with p-thiocresol attests to the lower electrophilicity of the 2 position, particularly as compared with the corresponding positions in the oxygen- and sulfur-containing analogs.



III XVI XV IV XVIII

Replacement of the ethyl residue attached to the nitrogen atom of 5-ethyl-3-phenazinone by a phenyl group leads to a decrease in the reactivity of the molecule. The reaction of 5-phenyl-3-phenazinone with p-thiocresol proceeds only when the mixture is heated. The solution is not decolorized, and the hydrogen atom in the 2 position of the quinoid ring is replaced under these conditions (XVIII).

Substitution in the 7 position does not occur even when 2-morpholino-5-phenyl-3-phenazinone (XIX) is refluxed with a fourfold excess of p-thiocresol for 10 h. In this case ~70% unchanged morpholino derivative (XIX) and ~30% 2-(p-tolylthio)-5-phenyl-3-phenazinone (XVIII) were isolated from the reaction mixture. The formation by 5-phenyl-3-phenazinone of only a product of monosubstitution in the 2 position of the quinoid ring even in the case of the use of a stronger nucleophile than amines indicates the absence of an electrophilic center in the benzenoid ring, the presence of higher electron density in the 2 and 7 positions, and, consequently, higher aromatic character of the molecule as a whole than in the case of compounds with S, O, and N–C_2H_5 heterobridges.

The decrease in the reactivity of the 7 position and of the molecule as a whole on passing from S, O, and N–R heterobridges can be explained for the O and N–R heterobridges (period II elements) by the different degrees of resonance interaction of the unshared pair of electrons of the atom with the π-electron system of the quinoid and benzenoid fragments [7]. The increased reactivity of the benzenoid ring in the case of phenothiazinone is probably associated with the manifestation by the sulfur atom of electron-acceptor properties owing to the presence of a vacant d orbital.

The noted change in the regularity of the effect of a second heterobridge (S, O, N–C_2H_5, and N–C_6H_5) or the change in the reactivities of I-IV is also retained in other solvents (benzene and DMF), and the rate of reaction of the compounds with p-thiocresol increases on passing from benzene to alcohol and DMF. The presence of catalytic amounts of concentrated hydrochloric acid also promotes an increase in the reaction rate.

Thus the results of the reaction of 3-phenothiazinone, 3-phenoxazinone, and 5-ethyl- and 5-phenyl-3-phenazinones with p-thiocresol show that there are two reactions centers – in the para position relative to the imine nitrogen atom in the benzenoid ring and in the 2 position in the quinoid ring – in sulfur-, oxygen-, and N-ethyl-containing heterocyclic quinones, whereas the N-phenyl analog contains only one reaction center in the quinoid ring.

The differences in the reactivities of these positions are due to the nature of the two heterobridges, which can be arranged in the order S, O, N–C_2H_5, and N–C_6H_5 with respect to their effect on the decrease in the electrophilicity of the 7 position.

EXPERIMENTAL

The electronic spectra of $5 \cdot 10^{-4}$ mole/liter solutions of V-VIII and XIV-XVIII in chloroform in the visible region were recorded with a Specord UV-vis spectrophotometer. The PMR spectra solutions of I and V-VII in dimethyl sulfoxide (DMSO) were recorded with a Perkin–Elmer R-12B spectrometer at 140°C. The R_f values were determined on Silufol UV-254 in benzene–ether (3:1)

7-(p-Tolylthio)-3-phenothiazinone (V), 2-(p-Tolylthio)-3-phenothiazinone (VI), and 2,7-Bis(p-Tolylthio)-3-phenothiazinone (VII). A) Five to six drops of concentrated HCl and 2.3 g (19 mmole) of p-thiocresol were added to 1.0 g (4.47 mmole) of 3-phenothiazinone (I) in 20 ml of alcohol, and the mixture was allowed to stand at room temperature for 1 h until a colorless solution of the hydroxy derivative formed. A freshly prepared solution (15 ml) of ferric chloride was then added with stirring, during which the solution turned red-brown. The solvent was removed by evaporation, and the residue was dissolved in ethyl acetate (3:1). The first reddish-brown fraction was collected, the solvent was removed by evaporation, and the residue was crystallized to give 0.32 g (15%) of VII. The second reddish-brown fraction yielded 0.39 g (12.5%) of VI. Workup of the third dark-red fraction gave 0.4 g of 3-phenothiazinone (I). The fourth (crimson) fraction yielded 0.31 g (20%) of V.

B) A mixture of 1.0 g (4.47 mmole) of I, 2.3 g (19 mmole) of p-thiocresol, and 20 ml of ethanol was maintained at room temperature for 1.5 h, after which it was worked up, and the product was purified by method A to give 0.25 g (16%) of V, 0.39 g (25%) of VI, and 0.30 g (14%) of VII.

C) A 0.5-g (65%) sample of VII was obtained from 0.5 g (1.5 mmole) of 2-(p-tolylthio)-3-phenothiazinone (VI) and 0.74 g (6.0 mmole) of p-thiocresol in 19 ml of ethanol under conditions similar to those in experiment A.

D) A 0.5-g (65%) sample of VII was obtained from a mixture of 0.5 g (1.5 mmole) of 7-(p-tolylthio)-3-phenothiazinone (V) and 0.74 g (6 mmole) of p-thiocresol under conditions similar to those in experiment A.

E) A 0.5-g (65%) sample of VII was obtained from 0.5 g (1.5 mmole) of 7-morpholino-3-phenothiazinone (XI) and 0.74 g of p-thiocresol in 15 ml of alcohol in the presence of three to four drops of concentrated HCl after refluxing for 1 h and workup and purification by method A.

2-Morpholino-7-(p-tolylthio)-3-phenothiazinone (XIV). A 0.3-g (41%) sample of XIV was obtained from the first reddish-brown fraction from 0.5 g (1.6 mmole) of 2-morpholino-3-phenothiazinone (XII) and 0.74 g (6 mmole) of p-thiocresol in 15 ml of alcohol in the presence of three to four drops of concentrated HCl after refluxing for 7 h and workup and purification by method A. Workup of the second fraction gave 0.2 g of unchanged XII.

7-Hydroxy-3-phenothiazinone (XIII). A solution of 0.5 g (1.6 mmole) of 7-(p-tolylthio)-3-phenothiazinone (V) in 10 ml of 75% H_2SO_4 was heated at 140°C for 4 h, after which it was poured into 50 ml of water, and the aqueous mixture was extracted with chloroform. Evaporation of the solvent and crystallization of the residue gave 0.25 g (71%) of VIII, which was identical to the 7-hydroxy-3-phenothiazinone described in [6].

2-(p-Tolylthio)-5-ethyl-3-phenazinone (XV) and 2,7-Bis(p-tolylthio)-5-ethyl-3-phenazinone (XVI). A) Five to six drops of concentrated HCl and 2.2 g (17 mmole) of p-thiocresol were added to 1.0 g (4.5 mmole) of 5-ethyl-3-phenazinone (III) in 25 ml of alcohol, and the mixture was allowed to stand at room temperature for 6 h until a colorless solution of the hydroxy derivative formed. Air was then bubbled into the solution for 1 min, during which it turned reddish-brown. The solvent was removed by evaporation, and the residue was dissolved in benzene–ethyl acetate (3:1) and subjected to chromatography. Evaporation of the solvent from the first reddish-brown fraction and crystallization of the residue gave 0.15 g (7%) of XVI. The second fraction yielded 0.15 g (10%) of XV.

B) A 0.12-g (5.7%) sample of XVI and 0.15 g (10%) of XV were obtained from a mixture of 1.0 g (4.5 mmole) of III and 2.22 g (17 mmole) of p-thiocresol in 25 ml of alcohol under conditions similar to those in experiment A.

C) A 0.40-g (59%) sample of XVI identical to 5-ethyl-3-phenazinone obtained from III by methods A and B was obtained from a mixture of 0.5 g (14 mmole) of 2-(p-tolylthio)-5-ethyl-3-phenazinone (XV) and 1.1 g (86 mmole) of p-thiocresol under conditions similar to those in experiment A.

D) A mixture of 0.5 g (17 mmole) of 2-morpholino-5-ethyl-3-phenazinone (XVII) and 1.1 g (85 mmole) of

p-thiocresol in 15 ml of alcohol was refluxed on a water bath for 7 h, after which it was worked up and the product was purified by method A to give 0.6 g (73%) of XVI.

E) A 0.4-g (63%) sample of XV was obtained from a mixture of 0.5 g (17 mmole) of 2-morpholino-5-ethyl-3-phenazinone (XVII) and 0.55 g (42.5 mmole) of p-thiocresol under conditions similar to those in experiment D.

2-(p-Tolylthio)-5-phenyl-3-phenazinone (XVIII). A) Five to six drops of concentrated HCl and 2.2 g (17.5 mmole) of p-thiocresol were added to 1.0 g (45 mmole) of 5-phenyl-3-phenazinone (IV) in 25 ml of alcohol, and the mixture was refluxed on a water bath for 7 h. The solvent was then removed by evaporation, and the residue was dissolved in benzene–ether (3 : 1) and subjected to chromatography. A 0.26-g (17%) sample of XVIII was obtained from the first (reddish-brown) fraction after evaporation of the solvent and crystallization. Workup of the second (purple-red) fraction yielded 0.8 g of starting 5-phenyl-3-phenazinone.

B) A 0.20-g (13%) sample of XVIII was obtained from a mixture of 1.0 g (45 mmole) of IV and 2.2 g (17 mmole) of p-thiocresol in 25 ml of alcohol under conditions similar to those in experiment A.

C) A 0.72-g (8 mmole) sample of p-thiocresol and three to four drops of concentrated HCl were added to 0.5 g (15 mmole) of 2-morpholino-5-phenyl-3-phenazinone (XIX) in 20 ml of alcohol, and the mixture was refluxed on a water bath for 10 h. The solvent was then removed by evaporation, and the residue was dissolved in benzene–ethyl acetate (3 : 1) and subjected to chromatography. Workup of the first fraction gave 0.18 g (35%) of XVIII, whereas the second fraction yielded 0.28 g of unchanged 2-morpholino-5-phenyl-3-phenazinone.

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