RESEARCH ON THE CHEMISTRY OF PHENOXAZINES.

12.* REACTION OF 2-SUBSTITUTED 3-PHENOXAZINONES WITH THIOPHENOLS

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A third reaction center in the phenoxazinone molecule, viz., the 9 position in the benzenoid ring, was observed for the first time in the reaction of 3-phenoxazinone and its 2-hydroxy and 2-ethoxy derivatives with p-thiocresol. In conformity with this, 2,7,9-triarylthio derivatives are formed along with the usual 2,7-disubstituted derivatives of 3-phenoxazinone. The structures of the compounds obtained were confirmed by the PMR and EPR spectra and a number of chemical transformations.

Only isolated cases in which nucleophilic substitution of hydrogen occurs when groups that are capable of anionic stabilization are present have been described [2, 3]. During a study of the reaction of 2-substituted derivatives of 3-phenoxazinone with p-thiocresol we observed a new instance of replacement of a hydrogen atom rather than an OC_2H_5 group in the electrophilic center of the quinoneimine part of the 3-phenoxazinone.

It has been previously shown [4] that 3-phenoxazinone has two electrophilic centers, viz., the 2 position in the quinoneimine part and the 7 position in the benzenoid ring; a substituent in the electrophilic center of the benzenoid ring has a substantial effect on the nucleophilic substitution reaction [5].

In the present research we investigated the effect of groups in the quinoneimine ring that are capable of anionic stabilization (OH and OC_2H_5) on the reaction with p-thiocresol. It might have been expected that 2-hydroxy- (I) and 2-ethoxy-3-phenoxazinone (II) would react with p-thiocresol to give mono- or disubstitution products [nucleophilic substitution of the hydrogen in the 7 position and the ethoxy (hydroxy) group in the 2 position].

The reaction of 2-substituted 3-phenoxazinones (I, II) with p-thiocresol proceeds in alcohol in the presence of catalytic amounts of a mineral acid at 20°C. In the case of II a mixture of two substances that have only slightly different R_f values and contain, respectively, one or two arylthio groups (III and IV) is formed. The ethoxy group is retained in both compounds. However, monoarylthio derivative III is converted completely [judging from thin layer chromatography (TLC) and the yield] to bis(arylthio) derivative IV in the case of slight heating of the reaction products with excess p-thiocresol. This conversion takes place through a step involving the formation of reduced form IVa, which gives oxo compound IV upon oxidation with air oxygen or an alcohol solution of ferric chloride.

Replacement of two hydrogen atoms with simultaneous retention of the hydroxy group in the 2 position (V) also occurs in the reaction of 2-hydroxy-3-phenoxazinone (I) with p-thiocresol. This is indicated by the results of elementary analysis, the ability of the compound obtained to form saltlike products at the hydroxy group, and a number of chemical transformations. The reaction of the silver salt of hydroxy derivative V with ethyl iodide leads to a compound that is completely identical to 2-ethoxybis(p-tolylthio)-3-phenoxazinone (IV) (according to the melting point, IR and UV spectra, and TLC), i.e., the p-tolylthio groups in IV and V are in the same positions.

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*See [1] for Communication 11.

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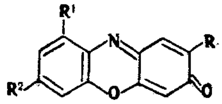
TABLE 1. p-Tolylthio Derivatives of 3-Phenoxazinone



Compound	R	R^1	R^2	mp, °C	λ_{max} (lg ε)	Found, %				Empirical formula	Calc., %				R_f	Yield, %
						C	H	N	S		C	H	N	S		
III	OC_2H_5	H	T^{a}	208–209^{b}	467 (4,45)	68,9	4,8	3,9	9,4	$C_{21}H_{17}NO_3S$	69,4	4,7	3,9	9,1	0,39	68
IV	OC_2H_5	T	T	239–240^{b}	481 (4,55)	69,5	4,8	2,8	13,3	$C_{28}H_{23}NO_3S_2$	69,3	4,7	2,9	13,2	0,48	10
V	OH	T	T	211–212^{c}	485 (4,45)	68,4	4,2	—	13,9	$C_{26}H_{19}NO_3S_2$	68,2	4,1	—	14,0	—	51
VI	NHC_6H_5	H	T	220–221^{b}	485 (4,50)	73,5	4,4	6,7	7,3	$C_{25}H_{18}N_2O_2S$	73,2	4,3	6,8	7,8	0,64^{d}	95
VII	Morpholino	H	T	221–222^{b}	485 (4,24)	67,9	4,9	7,2	7,7	$C_{23}H_{20}N_2O_3S$	68,3	4,9	6,9	7,9	0,31	90
IX	T	T	T	232–233^{b}	498 (3,47)	70,1	4,5	2,8	16,5	$C_{33}H_{25}NO_2S_3$	70,1	4,5	2,5	16,9	0,67	68

^{a}T = p-tolylthio. ^{b}From butyl alcohol. ^{c}From isoamyl alcohol. ^{d}The solvent was anhydrous chloroform; the R_f values for all of the remaining compounds were determined in a chloroform–acetone system (40:1).

The incorporation of two arylthio groups in 2-substituted 3-phenoxazinones with the simultaneous retention of the substituents in the electrophilic 2 position constitutes evidence for the presence of a third reaction center in the phenoxazinones. To determine its position we proved the structure of III-V by means of chemical transformations and data from PMR and EPR spectroscopy.

Products of replacement of the ethoxy group by an amino residue (VI and VII, Table 1) were obtained by reaction of 2-ethoxy(p-tolylthio)-3-phenoxazinone (III) with amines (aniline and morpholine). Compounds VI and VII in turn readily exchange the amino group in the 2 position for a p-tolylthio group upon subsequent reaction with p-thiocresol. Identical compounds, which, with respect to their R_f values, melting points, and IR and UV spectra, correspond to the previously described 2,7-bis(p-tolylthio)-3-phenoxazinone (VIII) [4], are formed in both cases. It hence follows that one p-tolylthio group in IV and V is also located in the 7 position in III.

Singlet signals of 4-H and 1-H protons, respectively, are observed in the PMR spectrum of III at 6.18 and 6.63 ppm. The 9-H proton absorbs in the weak-field part of the spectrum (7.6 ppm, $J_{9,6}$ = 1 Hz, and $J_{9,8}$ = 8 Hz). The doublet of doublets at 7.05 ppm is related to the signal of the 6-H proton ($J_{6,9}$ = 1 Hz, $J_{6,8}$ = 2 Hz). Some of the lines of the signal of the 8-H proton at 7.2-7.6 ppm are masked by the superimposition of the quartet of the AB type of the p-disubstituted aromatic protons of the p-tolylthio group, but $J_{8,6}$ = 2 Hz can be determined for one of the doublets.

Information regarding the position of the second arylthio group in IV and V was obtained by a comparison of the hfs constants of the EPR spectra* of the anion radicals generated by electrochemical reduction of these compounds with the values for the anion radicals of I and III [6] (Table 2). Thus the hfs from the 7-H and 9-H protons vanishes in the EPR spectrum on passing from the anion radical of I to the anion radical of V, and this indicates the presence of two substituents (arylthio groups) in these positions. It was similarly shown that the second arylthio group in IV is in the 9 position.

As in the case of III, the PMR spectrum of IV contains two singlet signals of 4-H and 1-H protons at 6.20 and 6.75 ppm. A multiplet from the superimposition of two AB quartets of the p-tolylthio group (8-H) is found at 7.1-7.4 ppm. The doublets at 6.38 and 6.67 ppm with J = 2 Hz are related to the meta protons of the benzene ring. Since one of the p-tolyl-

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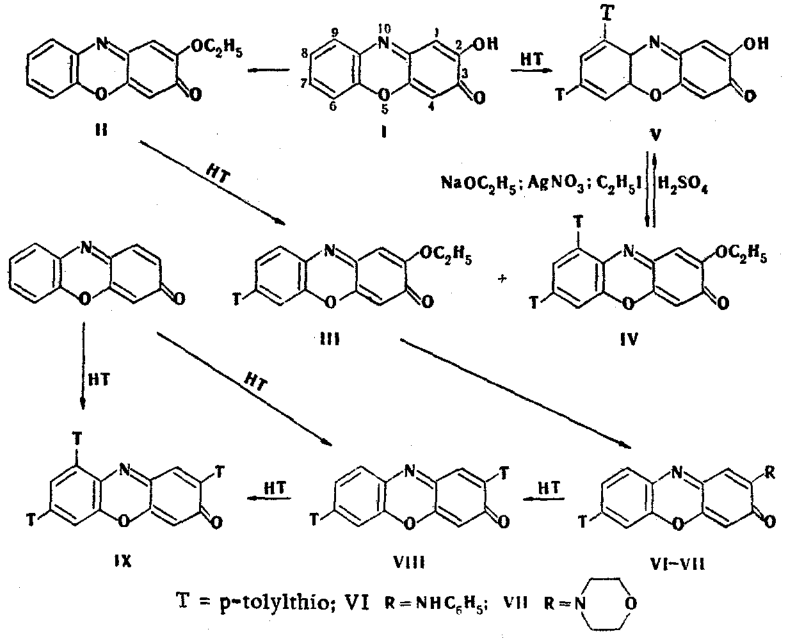
*A detailed study of the anion radicals of a number of substituted phenoxazinones will be published separately.

TABLE 2. hfs Constants (Oe) of the Anion Radicals (AR)

AR of compound	aN	aH (1)	aH (4)	aH (6)	aH (7)	aH (8)	aH (9)	aH OC_2H_5
I [6]	4,04	—	—	0,44	1,64	0,44	1,64	—
V	3,10	—	—	0,46	—	0,46	—	—
III [6]	5,64	0,58	—	0,58	—	0,58	2,20	0,58
IV	5,60	0,60	—	0,60	—	0,60	—	0,60

thio groups is in the 7 position, there can be two protons in the meta position only when a substituent is present in the 9 position.

Thus, the third reaction center in 2-substituted 3-phenoxazinones is the 9 position in the benzenoid part of the molecule, i.e., in the nucleophilic substitution of 2-substituted 3-phenoxazinones with thiophenols replacement of the hydrogen atom not only in the 7 position, but also in the 9 position, proceeds more readily than replacement of the ethoxy group in the electrophilic center of the quinoneimine ring, which is replaced smoothly in reactions with amines [1]. The results make it possible to assume that hydrogen is not split out in the form of a hydride ion in the nucleophilic substitution of 2-substituted 3-phenoxazinones with thiophenols.



T = p-tolylthio; VI R = NHC_6H_5; VII R = N O

The detection of a third reaction center in 3-phenoxazinones that contain a hydroxy or ethoxy group in the 2 position allows for the possibility of the formation of 9-arylthio derivatives also in the case of the reaction with thiophenols of other 3-phenoxazinones, including unsubstituted 3-phenoxazinone, for which only mono- and disubstitution products involving the 2 and 7 positions were previously obtained [4]. In fact, when 2,7-bis(p-tolylthio)-3-phenoxazinone (VIII) is heated in alcohol with excess p-thiocresol, it gives a slightly colored solution of the reduced form, which upon oxidation is rapidly converted to 2,7,9-tris(p-tolylthio)-3-phenoxazinone (IX), which contains three arylthio groups. Under severe conditions with excess p-thiocresol, IX can also be obtained from 3-phenoxazinone.

EXPERIMENTAL

The electronic spectra were recorded with a Specord spectrophotometer. The PMR spectra of solutions of d_6-DMSO at 140°C were recorded with a Perkin–Elmer P12A spectrometer. The EPR spectra were recorded with a Sibir' ÉPR-3 spectrometer. The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates.

The anion radicals of IV and V were generated electrochemically in DMSO directly in the resonator of the EPR spectrometer. The concentration of the starting compounds was $5 \cdot 10^{-3}$ M; tetraethylammonium perchlorate (0.1 M) was used as the support electrolyte.

2-Hydroxy-3-phenoxazinone was obtained by the method in [7], and 2-ethoxy-3-phenoxazinone was obtained by the method in [1, 8].

7-(p-Tolylthio)-2-ethoxy-3-phenoxazinone (III) and 7,9-Bis(p-tolylthio)-2-ethoxy-3-phenoxazinone (IV). A) A 0.7-g (4.0 mmole) sample of p-thiocresol and four drops of concentrated HCl were added to a suspension of 0.5 g (2.1 mmole) of 2-ethoxy-3-phenoxazinone in 20 ml of ethanol, and the mixture was heated on a water bath until the starting compounds dissolved and a light-green solution of the reduced form was obtained. This solution was then cooled. For oxidation of the reduced form, 8 ml of a 10% alcohol solution of ferric chloride was added with stirring, and the mixture was allowed to stand for 8-10 h. The resulting precipitate was removed by filtration, washed with alcohol, and chromatographed with a column filled with KSK silica gel (elution with anhydrous chloroform). The first (orange) and second (red) fractions were collected, and the solvent was removed to give, respectively, 0.3 g of III and 0.1 g of IV (Table 1).

Only IV was obtained in quantitative yield when the reaction mixture was heated for 2 h.

B) A 0.3-g (0.7 mmole) sample of V was suspended in an alcohol solution of sodium ethoxide, prepared from 0.4 g of sodium and 20 ml of absolute alcohol, and the mixture was heated on a water bath for 20 min. The precipitated sodium salt was removed by filtration, dried, and dissolved in distilled water. An aqueous solution of 0.2 g of silver nitrate was added, and the flocculent precipitate was removed by filtration, washed with water, and dried. Ethanol (10 ml) and 2 ml of ethyl iodide were added to the dry silver salt of V, and the mixture was refluxed for 2 h. The precipitated silver iodide was removed by filtration, the filtrate was cooled, and the precipitate was removed by filtration, dried, and chromatographed with a column filled with activity II Al_2O_3 (elution with benzene). The orange fraction was collected, and the solvent was removed by distillation to give IV in 60% yield.

2-Anilino-7-(p-tolylthio)-3-phenoxazinone (VI). Aniline (1 ml) was added to 0.2 g (0.55 mmole) of 2-ethoxy-7-(p-tolylthio)-3-phenoxazinone (III) in 10 ml of ethanol, and the mixture was refluxed for 2 h. It was then cooled, and the precipitate was removed by filtration, washed with alcohol, and crystallized to give 0.17 g of VI (Table 1).

2-Morphilino-7-(p-tolylthio)-3-phenoxazinone (VII). A 1.6-ml sample of morpholine and 0.1 g of morpholine hydrochloride were added to a suspension of 0.1 g (0.27 mmole) of III in 5 ml of alcohol, and the mixture was refluxed for 8 h. It was then cooled, and the precipitate was removed by filtration, washed with water and alcohol, and crystallized to give 0.08 g of VII (Table 1).

7,9-Bis(p-tolylthio)-2-hydroxy-3-phenoxazinone (V). A 0.9-g (7.3 mmole) sample of p-thiocresol and five drops of concentrated HCl were added to a suspension of 0.5 g (2.4 mmole) of I in 20 ml of alcohol, and the mixture was allowed to stand at room temperature for 70 h. The initially formed light-green solution gradually turned dark brown due to oxidation with air oxygen. The precipitate was removed by filtration, washed with alcohol, and crystallized. The yield was 0.64 g (Table 1).

2,7-Bis(p-tolylthio)-3-phenoxazinone (VIII) and 2,7,9-Tris(p-tolylthio)-3-phenoxazinone (IX). A 0.1-g (0.8 mmole) sample of p-thiocresol and three drops of concentrated HCl were added to a suspension of 0.14 g (0.35 mmole) of VII (or VI) in 15 ml of ethanol, and the mixture was refluxed for 4 h. It was then cooled and treated with 5 ml of a 10% alcohol solution of ferric chloride. The precipitate was removed by filtration, washed with alcohol, dried, and chromatographed with a column filled with activity II Al_2O_3 (elution with benzene). The first (red) fraction was collected and worked up to give 0.07 g (46%) of VIII. Removal of the solvent from the second (violet) fraction by distillation gave 0.1 g of IX (Table 1).

LITERATURE CITED

1. G. B. Afanas'eva, I. Ya. Postovskii, and T. S. Viktorova, Khim. Geterotsikl. Soedin., No. 9, 1120 (1978).
2. O. N. Chupakhin and I. Ya. Postovskii, Usp. Khim., 45, 908 (1976).
3. K. Kurita and R. L. Williams, J. Heterocycl. Chem., 14, 673 (1977).
4. K. I. Pashkevich, G. B. Afanas'eva, and I. Ya. Postovskii, Khim. Geterotsikl. Soedin., No. 6, 746 (1971).
5. G. B. Afanas'eva, T. S. Viktorova, K. I. Pashkevich, and I. Ya. Postovskii, Khim. Geterotsikl. Soedin., No. 3, 348 (1974).

6. I. I. Vil'kis, E. G. Boguslavskii, T. S. Viktorova, G. B. Afanas'eva, I. Ya. Postovskii, and S. M. Shein, Summaries of Papers Presented at the Third All-Union Conference on Charge-Transfer Complexes and Ion-Radical Salts [in Russian], Zinatne, Riga (1976), p. 92.
7. O. Fischer and O. Jonas, Ber., 27, 2782 (1894).
8. E. Ruzicka and J. Yurina, Monatsh., 97, 139 (1966).

FUNCTIONAL DERIVATIVES OF THIOPHENE.

18.* SYNTHESIS OF 4-OXOTHIENO[2,3-d]OXAZINE DERIVATIVES AND THIOPHENE-3-CARBOXYLIC ACID HYDRAZIDES

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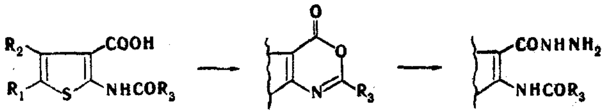
2-Aryl-4-oxothieno[2,3-d]oxazine derivatives were synthesized. Opening of the oxazine ring to give 2-benzamidothiophene-3-carboxylic acid hydrazide derivatives is observed when these compounds are treated with hydrazine hydrate.

We have found that 4-oxothieno[2,3-d]oxazines (IIa-h) can be obtained by the action of thionyl chloride on 2-aroylaminothiophene-3-carboxylic acids (Ia-h) in the presence of dimethylformamide (DMF), i.e., under the conditions of the synthesis of arenecarboxylic acid chlorides. The reaction evidently proceeds through a step involving the formation of thiophenecarboxylic acid chlorides. We obtained thiophenecarboxylic acids Ia, c, h for the first time by the method described in [2].

In the reaction of 2-aryl-4-oxothieno[2,3-d]oxazines (IIb-e, g) with hydrazine hydrate we observed opening of the oxazine ring to give 2-benzamidothiophene-3-carboxylic acid hydrazides (IIIb-e, g).

One absorption band of a carbonyl group is observed in the IR spectra of IIa-h at 1750-1760 cm^{-1}; in addition, the absorption bands of a hydroxy group at 2550-2600 cm^{-1} and of an amide group at 3140-3300 (NH) and 1640-1650 cm^{-1} (CO) that are characteristic for starting thiophene-3-carboxylic acids Ia-h vanish. Several absorption bands of stretching vibrations of an NH bond that characterize a primary amino group and a secondary amide are observed in the spectra of hydrazides IIIb-e, g at 3180-3300 cm^{-1}. The absorption of the carbonyl groups (CO) shows up in the form of one absorption band at 1640-1650 cm^{-1}. The shift of the absorption bands of the carbonyl groups in the low-frequency region is evidently explained by the development of hydrogen bonds. A similar pattern in the IR spectra is observed for 2-acylaminothiophene-3-carboxylic acids.



I a-h   II a-h   III b-e, g

I—III a $R_1=H$, $R_2=C_4H_3S$, $R_3=C_6H_5$, b $R_1=CH_3$, $R_2=H$, $R_3=C_6H_5$. c $R_1=C_2H_5$, $R_2=H$, $R_3=C_6H_5$, d $R_1=R_2=CH_3$, $R_3=C_6H_5$, e $R_1=R_2=(CH_2)_4$, $R_3=C_6H_5$, f $R_1R_2=(CH_2)_4$, $R_3=p\text{-}C_6H_4CH_3Cl$, g $R_1=H$, $R_2=R_3=C_6H_5$, h $R_1=H$, $R_2=C_6H_5$, $R_3=p\text{-}C_6H_4Cl$

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*See [1] for Communication 17.

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