INVESTIGATION OF THE CHEMISTRY OF PHENOXAZINES

V.* NUCLEOPHILIC ADDITION TO BENZOPHENOXAZINONES AS A FUNCTION OF THE POSITION OF THE ANNELATED BENZENE RING

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Depending on the position of the annelated benzene ring, benzophenoxazinones add thiophenols in the benzenoid, quinonoid, or both parts of the molecule to give mono- or diarylmercapto derivatives. A substituent in the benzenoid portion of the molecule hinders polarographic reduction and shifts the visible absorption band bathochromically, while a substituent in the quinonoid portion has practically no effect on the $E_{1/2}$ value.

The 3-phenoxazinone (I) molecule has two electrophilic centers [1] – in the benzenoid and quinonoid rings – to which the addition of nucleophiles can occur. The annelation of 3-phenoxazinone may not only block one of the electrophilic centers but also can substantially affect [2] the π-electron structure and thereby the reactivity of the molecule.

In the present paper we have investigated the addition of thiophenols to benzophenoxazinones (II-V) with an annelated ring in different positions.

Benzo[*a*]phenoxazin-9-one (II) and benzo[c]phenoxazin-3-one (III) contain a benzene ring annelated with the benzenoid portion of the molecule, and in III this benzene ring covers the electrophilic center of the molecule – the p position relative to the heterocyclic nitrogen atom. The quinonoid ring in both compounds is open to attack, as in nonannelated I. However, it has been reported [3-5] only that nucleophiles add to the benzenoid portion of II in the p position relative to the nitrogen atom, while the reactions of III have not been described at all.

In an investigation of the reaction of benzo[*a*]phenoxazin-9-one with thiophenols, it was found that the major products under severe (as compared with those in [6]) conditions (prolonged refluxing in alcohol) are diarylmercapto derivatives of II (XII-XIV, Table 1), and 5-arylmercaptobenzo[*a*]phenoxazin-9-ones [6] (IX-XI) are formed only in small amounts. In contrast to the reaction of thiophenols with 3-phenoxazinone [1], in the case of II the isomeric products of monoaddition to the quinonoid portion of the molecule were not isolated, and not even traces of these products were detected upon investigation of the reaction mixture by means of thin-layer chromatography (TLC). These observations, as well as the literature data [3-6], demonstrate that annelation of the benzenoid portion of the I molecule in the [*a*] manner to a considerable degree increases the electrophilicity of the p position relative to the heterocyclic nitrogen atom in the benzenoid portion and decreases the electrophilicity of the reaction center in the quinonoid ring.

* See [1] for communication IV.

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TABLE 1. Arylmercapto Derivatives of Benzophenoxazinones II-V

Compound	Reaction time, h	mp, °C (crystallization solvent)	R_f* a	R_f* b	Empirical formula
XII	5—6	298—299 (pyridine)	0,571	0,490	$C_{30}H_{21}NO_2S_2$
XIII	8—9	282—283 (pyridine, aqueous dimethylformamide)	0,557	0,491	$C_{28}H_{17}NO_2S_2$
XIV	15—16	279—280 (dimethylformamide)	0,507	0,494	$C_{28}H_{15}N_3O_6S_2$
XV	2—3	249—250 (butanol)	0,638	0,425	$C_{23}H_{15}NO_2S$
XVI	5—6	241—242 (butanol)	0,614	0,453	$C_{22}H_{13}NO_2S$
XVII	10—11	295—296 (pyridine)	0,571	0,378	$C_{22}H_{11}N_2O_4S$
XVIII	72	225—226 (butanol)	0,607	0,617	$C_{24}H_{17}NO_2S$
XIX	72	207—208 (butanol)	0,555	0,549	$C_{23}H_{15}NO_2S$
XX	8—9	196—197 (pyridine + water)	0,561	0,500	$C_{23}H_{15}NO_2S$
XXI	12—15	194—195 (pyridine + alcohol)	0,657	0,444	$C_{22}H_{13}NO_2S$
XXII	22—24	240—241 (pyridine)	0,647	0,396	$C_{22}H_{11}N_2O_4S$

TABLE 1 (continued)

Compound	Found, % C	Found, % H	Found, % N	Found, % S	Calc., % C	Calc., % H	Calc., % N	Calc., % S	Yield, %
XII	73,5	4,2	—	13,1	73,4	4,3	—	13,0	40
XIII	—	—	3,1	13,9	—	—	3,0	13,8	36
XIV	—	—	—	10,9	—	—	—	11,5	27
XV	74,9	4,3	3,9	8,9	74,7	4,1	3,8	8,7	28
XVI	74,6	3,6	4,3	8,6	74,4	3,7	4,0	9,0	30
XVII	—	—	7,0	8,0	—	—	7,0	8,0	22
XVIII	75,4	4,5	3,8	8,5	75,3	4,5	3,6	8,4	37
XIX	75,4	4,1	—	8,7	74,9	4,1	—	8,7	40
XX	—	—	3,9	9,0	—	—	3,8	8,7	32
XXI	—	—	4,0	9,0	—	—	4,0	9,0	34
XXII	—	—	7,3	8,4	—	—	7,0	8,0	26

*On activity II aluminum oxide in the following systems: a) benzene—alcohol (9 : 1); b) anhydrous chloroform—alcohol (98 : 2).

Benzo[c]phenoxazin-3-one contains an electrophilic position only in the quinonoid ring. The annelated ring in this case is a weak electron donor [2] and only slightly decreases the electron-acceptor character of III as compared with I. In conformity with this, benzo[c]phenoxazin-3-one adds only one molecule of thiophenol in the quinonoid portion (XV-XVII, Table 1). An increase in the temperature leads only to acceleration of the reaction rather than to the addition of a second molecule of thiophenol, as in the reaction of II.

A benzene ring annelated to the quinonimine portion of 3-phenoxazinone is the strongest electron donor [2] of all of the angularly condensed benzene rings. Owing to this, benzo[*a*]phenoxazin-5-one (V) enters with difficulty into the reaction with thiophenols (the reaction proceeds only on prolonged refluxing in alcohol and requires the addition of catalytic amounts of hydrochloric acid) and adds only one molecule of thiophenol to give XX-XXII (Table 1). The addition proceeds at the 9 position of the molecule, as proved

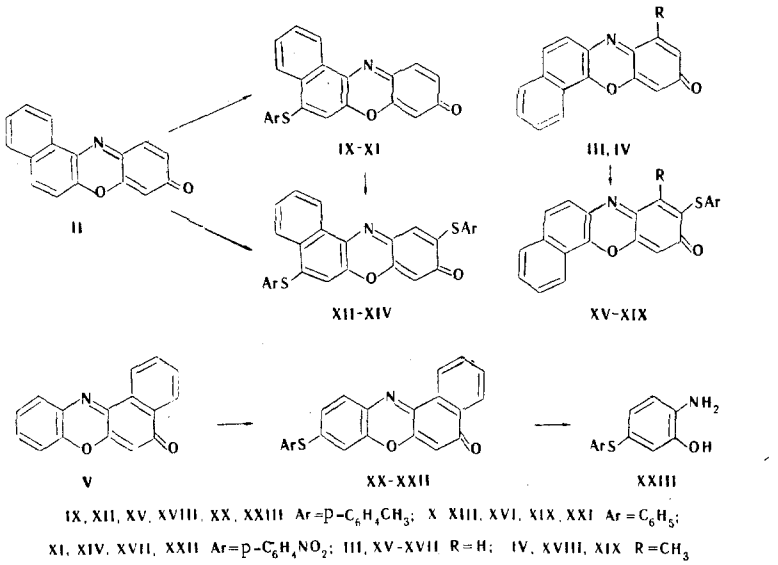
TABLE 2. Polarographic and Spectral Characteristics of Arylmercapto Derivatives of Phenoxazinones*

Compound	Visible spectrum		Half-wave potentials and limiting-current constants					
			in methanol		in dimethylformamide			
	λ_{max} (nm)	lg ε	$E_{1/2}$†	K	$E'_{1/2}$†	$E''_{1/2}$	K_1	K_2
VI	482 (447)	4,40 (4,15)	−0,70 (−0,55)	5,1 (5,2)	−0,79 (−0,63)	−1,14 (−1,00)	— —	— —
VII	433	4,51	−0,54	—	−0,62	−1,01	—	—
VIII	486	4,59	−0,69	—	−0,71	−1,24	—	—
IX	533 (498)	4,54 (4,30)	−0,76 (−0,60)	— —	−0,77 (−0,63)	−1,09 (−1,08)	1,2 (1,3)	0,9 (1,4)
XII	531	4,02	−0,76	—	−0,77	−1,08	—	—
XV	470 (501)	4,39 (4,14)	−0,58 (−0,51)	— —	−0,68 (−0,65)	−1,14 (−1,01)	1,1 (1,5)	0,8 (1,3)
XVIII	494 (498)	4,39 (4,20)	−0,57 (−0,60)	— —	−0,62 (−0,60)	−0,94 (−0,93)	— —	— —
XX	467 (432)	4,48 (4,18)	−0,82 (−0,75)	5,2 (4,7)	−0,79 (−0,79)	−1,19 (−1,12)	1,5 (1,4)	1,2 (1,4)

* The corresponding values for unsubstituted phenoxazinones are presented in parentheses.

† These are the $E_{1/2}$ values relative to a saturated calomel electrode.

by the alkaline decomposition of 9-tolylmercaptobenzo[a]phenoxazin-5-one. The reaction yielded 3-hydroxy-4-aminophenyl-4'-tolyl sulfide (XXIII), which was identical to that reported in [1].



IX, XII, XV, XVIII, XX, XXIII Ar = p-$C_6H_4CH_3$; X XIII, XVI, XIX, XXI Ar = C_6H_5; XI, XIV, XVII, XXII Ar = p-$C_6H_4NO_2$; III, XV-XVII R = H; IV, XVIII, XIX R = CH_3

In [1] it was established that the introduction of an arylmercapto residue into the benzenoid portion of I causes a bathochromic shift of the visible band of the spectrum, while introduction into the quinonoid portion induces a hypsochromic shift. A comparison of the visible absorption spectra of the arylmercapto derivatives with the spectra of the corresponding starting benzophenoxazinones (II and V) (Table 2) also confirms the dependence of the position of the visible band on the site of entry of the substituent. In the case of arylmercapto derivatives of benzo[c]phenoxazin-3-one, there is a hypsochromic shift of the visible band in the electronic spectrum as compared with starting III, and one can therefore assume, with a high degree of probability, that the arylmercapto residue enters the quinonoid ring of benzo[c]phenoxazin-3-one.

It is known that the position and nature of the substituent in several 3-phenoxazinone derivatives have a substantial effect on the $E_{1/2}$ value during polarographic reduction. In the case of arylmercapto derivatives of phenoxazinones (VI-IX, XII, XV, XVIII, and XXI, Table 2), the polarographic reduction is similar in quantity, character of the polarographic waves, and limiting-current values to the polarographic reduction of unsubstituted phenoxazinones and proceeds as a two-electron one-step process in proton-

donor media (dimethylformamide). The introduction of arylmercapto groups into the quinonoid portion of the molecule has practically no effect on the half-wave potential ($E_{1/2}$) in methanol and $E_{1/2}$ in dimethylformamide, while the introduction of an arylmercapto group into the benzenoid portion of the molecule somewhat hinders the polarographic reduction.

To establish the site of entry of the nucleophile into the quinonoid ring of phenoxazinones, we synthesized 1-methylbenzo[c]phenoxazin-3-one (IV) by condensation of α-naphthol with 3-methyl-4-nitrosophenol. The proposed method of synthesis differs favorably from that described in [7] with respect to the higher yield and more accessible starting materials. It was found that 1-methylbenzo[c]phenoxazin-3-one, like benzo[c]phenoxazin-3-one, reacts with thiophenols to give monoaddition products (XVIII and XIX, Table 1). The addition of thiophenols to IV is hindered as compared with the addition to III and occurs under the influence of a large excess of the thiophenol and with heating.

Since benzo[*a*]phenoxazin-5-one, in the quinonoid ring of which only the 4 position is free, does not add thiophenols in the quinonoid portion, while 1-methylbenzo[c]phenoxazin-3-one, in the quinonoid portion of which the 2 and 4 positions are free, reacts with thiophenols, it can be assumed that the entry of thiophenols into the quinonoid ring of phenoxazinones proceeds in the 2 position.* The retarded addition to IV as compared with III is probably associated with steric hindrance to addition at the 2 position.

EXPERIMENTAL

Benzo[*a*]phenoxazin-9-one (II) was obtained by the method in [3], benzo[c]phenoxazin-3-one (III) was prepared by the method in [8], and benzo[*a*]phenoxazin-5-one (V) was obtained by the method in [9].

7-Tolylmercapto-3-phenoxazinone (VI), 2-tolylmercapto-3-phenoxazinone (VII), and 2,7-ditolylmercapto-3-phenoxazinone (VIII) were obtained via the method in [1].

1-Methylbenzo[c]phenoxazin-3-one (IV). This compound was obtained from 29 g (0.2 mole) of α-naphthol and 41 g (0.3 mole) of 3-methyl-4-nitrosophenol. The condensation and isolation of IV were carried out as described in [8] for III. The yield of IV with mp 240-242° (from butanol) (mp 230-232° [7]) and R_f 0.473 on activity II Al_2O_3 with elution by anhydrous chloroform–alcohol (9 : 1) was 2.5-3 g (6%). Found: C 78.5; H 4.3; N 5.6%. $C_{17}H_{11}NO_2$. Calculated: C 78.2; H 4.3; N 5.6%.

5-Tolylmercaptobenzo[*a*]phenoxazin-9-one (IX) and 5,10-Di(tolylmercapto)benzo[*a*]phenoxazin-9-one (XII). Five to six drops of concentrated hydrochloric acid and 1 g (0.008 mole) of p-thiocresol were added to 1 g (0.004 mole) of benzo[*a*]phenoxazin-9-one (II) in 25 ml of alcohol, and the mixture was heated on a water bath at 60-65° for 3-4 h. Another 0.3 g of p-thiocresol and 2 drops of concentrated hydrochloric acid were added, and the mixture was refluxed for 2 h. To complete the oxidation, 10 ml of a freshly prepared 10% alcohol solution of $FeCl_3$ was added, and the mixture was stirred and refluxed on a water bath for 15 min. It was then cooled, and the precipitate was removed by filtration and washed with alcohol. The dried precipitate was dissolved in chloroform and chromatographed in two columns (25 by 500) filled with activity II Al_2O_3 with elution by anhydrous chloroform. The first violet fraction was collected and evaporated, and the residue was crystallized to give 0.9-1 g of XII. The second violet fraction was collected and evaporated, and the residue was crystallized to give 0.1-0.15 g of IX.

2-Tolylmercaptobenzo[c]phenoxazin-3-one (XV). Three drops of concentrated hydrochloric acid and 0.3 g (0.0024 mole) of p-thiocresol were added to 0.45 g (0.002 mole) of benzo[c]phenoxazin-3-one (III) in 10 ml of alcohol, and the mixture was stirred at room temperature for 1 h, after which another 0.1 g of p-thiocresol was added, and the mixture was stirred until the red-brown color of the solution changed completely to the light-green color characteristic for the leuco compound. The leuco compound was oxidized by the addition of 10 ml of a 10% aqueous alcohol solution of $FeCl_3$. The precipitated crystals were removed by filtration, washed with water, alcohol, and ether, and dried. Purification gave 0.2-0.3 g of XV.

1-Methyl-2-tolylmercaptobenzo[c]phenoxazin-3-one (XVIII). A mixture of 0.2 g of 1-methylbenzo[c]-phenoxazin-3-one (IV), 0.2 g of p-thiocresol, 5 ml of alcohol, and two drops of concentrated hydrochloric acid was allowed to stand for 2 days with stirring from time to time. It was then heated on a water bath for 3 h and allowed to stand for another day. The mixture was oxidized with an alcoholic solution of $FeCl_3$. The precipitate was removed by filtration and purified to give 0.1-0.15 g of XVIII.

* Rather than in the 1 position as previously assumed [1] for 3-phenoxazinone on the basis of an analysis of the π-electron distribution.

9-Tolylmercaptobenzo[*a*]phenoxazin-5-one (XX). A 1-g (0.005 mole) sample of thoroughly ground benzo[*a*]phenoxazin-5-one was suspended in 50 ml of alcohol, 10-12 drops of concentrated hydrochloric acid and 0.2 g (0.0016 mole) of p-thiocresol were added, and the mixture was slowly brought to the boiling point and refluxed for 2 h on a water bath. Two drops of concentrated hydrochloric acid and 0.2 g of p-thiocresol were then added, and the mixture was refluxed for another 2 h. The operation was repeated twice, and the reaction mass was then cooled, filtered, washed with alcohol and ether, and chromatographed with a column filled with Al_2O_3 to give 0.7-0.8 g of XXI.

The addition of thiophenol and p-nitrothiophenol to II leads to X, XIII and XI, XIV; to III and IV leads to XVI, XIX, and XVI; and to V leads to XXI and XXII. The reaction was carried out as in the addition of p-thiocresol to the appropriate benzophenoxazinone. The reaction times are presented in Table 1. In the addition of p-nitrothiophenol, the reaction was carried out in alcohol–chloroform (3 : 1).

3-Hydroxy-4-aminophenyl 4'-Tolyl Sulfide (XXIII). A 0.4-g sample of XX was moistened with three drops of alcohol, 10 ml of 4 N aqueous sodium hydroxide was added, and the mixture was heated under argon on a boiling-water bath until the spot of the starting XXI had disappeared completely on the thin-layer chromatogram (Al_2O_3 with elution with anhydrous chloroform). Isolation and purification according to the method in [1] gave 0.03 g (12%) of XXIII with mp 109-110°. Found: C 67.5; H 5.6; S 13.9%. $C_{13}H_{13}NOS$. Calculated: C 67.7; H 5.6; S 13.8%. The melting point of a mixture of this product with 3-hydroxy-4-aminophenyl 4'-tolyl sulfide, obtained by the method in [1], was 108-109°.

The visible spectra of chloroform solutions (c 10^{-4} M) were recorded with an SF-10 spectrophotometer. The polarographic measurements were carried out with an LP-60 recording polarograph in a thermostatted electrolytic cell with an internal anode. The backgrounds were 0.1 N solutions of $LiClO_4$ in methanol and dimethylformamide. The capillary had the following characteristics: $\tau = 1.85$ sec, $m = 1.61$ mg/sec (when the circuit was broken in the background solution).

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