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RESEARCH IN THE CHEMISTRY OF PHENOXAZINES.

XI.* REACTION OF 2-SUBSTITUTED 3-PHENOXAZINONES WITH AMINES

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The 2 position of the quinoid ring undergoes nucleophilic substitution in the reaction of 2-acetoxy- and 2-ethoxy-3-phenoxazinones with amines. In the case of 2- and 7-substituted derivatives of 3-phenoxazinone, replacement of a hydrogen atom or groups in the electrophilic center of the quinoid ring proceeds more readily than attack by the nucleophile on the 7 position in the benzo ring.

It is known [2] that nucleophilic substitution in benzo[a]-9-phenoxazinone takes place in the para position relative to the nitrogen atom in the naphthalene fragment. At the same time, our research has shown that 3-phenoxazinone has two electrophilic centers — the para position relative to the nitrogen atom in the benzenoid portion and the 2 position in the quinoneimine portion of the molecule [3].

Nucleophilic substitution of hydrogen (subsequently designated as S_NH [4]) primarily occurs in the 2 position of the quinoid ring in the reaction of nucleophiles with 3-phenoxazinone derivatives with substituents in the electrophilic center of the benzene ring (the 7 position). Strongly nucleophilic amines are capable of displacing a substituent in the 7 position [5]. This indicates that the S_NH reaction takes place more readily in the 2 position than substitution in the 7 position.

In order to draw some conclusion as to which positions are more reactive with respect to nucleophiles in both S_NH and S_N reactions, in the present research we investigated nucleophilic substitution reactions in the case of 3-phenoxazinone derivatives with substituents in the electrophilic center of the quinoid ring.

2-Hydroxy-3-phenoxazinone (I) [6], which displays weak acidic properties (its pK_a is 6.48 [7]), behaves specifically with amines. It was demonstrated by spectroscopy that I gives only unstable complexes on reaction with amines. An absorption maximum at 505 nm, which corresponds to the 2-hydroxy-3-phenoxazinone anion, obtained by dissolving the sodium salt of I, appears in the electronic absorption spectrum of an alcohol solution of a mixture of I with morpholine. This indicates the saltlike character of complexes of 2-hydroxy-3-phenoxazinone with amines. The formation of an anion naturally hinders S_N reaction of I with amines.

The reaction of 2-acetoxy- (II) [8] and 2-ethoxy-3-phenoxazinones (III) with amines proceeds in a different manner. The result of the reaction of 2-acetoxy-3-phenoxazinone with amines depends markedly on the nucleophilicity of the latter. Replacement of the acetoxy group to give 2-arylamino-3-phenoxazinones (IV-V) occurs in the reaction of II with arylamines. The rate of the competitive deacetylation of 2-acetoxy-3-phenoxazinone, which leads to hydroxy compound I, increases as the nucleophilicity of the arylamine increases, and the yield of the substitution product decreases (Table 1). Thus only 2-hydroxy-3-phenoxazinone is formed in the reaction of II with p-toluidine (pK_a 5.12). Similarly, hydroxy compound I is also formed in the reaction of 2-acetoxy-3-phenoxazinone with N-methylaniline and cycloalkylimines.

*See [1] for communication X.

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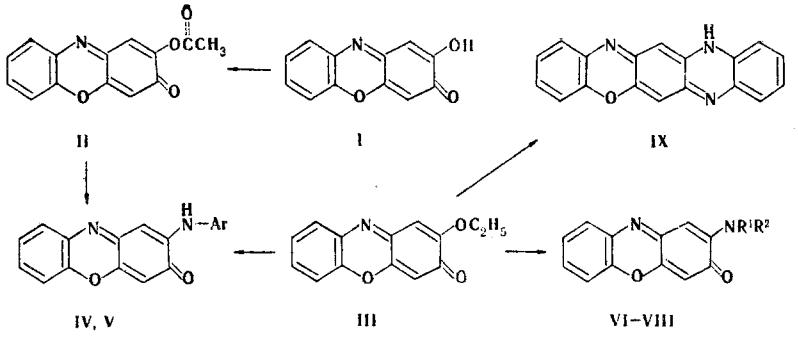
TABLE 1. 2-Arylamino-3-phenoxazinones

Compound	mp, °C (crystallization solvent)	Found, %			Empirical formula	Calc., %			R_f	Yield, %
		C	H	N		C	H	N		
IV	211—212 (ethanol)	74,2	4,4	10,0	$C_{18}H_{12}N_2O_2$	74,6	4,2	9,7	0,35	11
V	>350 (dimethylformamide)	65,4	3,4	13,6	$C_{18}H_{11}N_3O_4$	65,8	3,3	13,6	0,48	77
VI	211—212 (butanol)	75,2	4,4	9,3	$C_{19}H_{14}N_2O_2$	75,5	4,7	9,3	0,42	76

It is known [9] that the alkaline cleavage of aryl alkyl ethers to the corresponding phenols takes place under severe conditions, and it therefore might have been expected that even amines with high nucleophilicities would not bring about dealkylation of 2-ethoxy-3-phenoxazinone, which is resistant to nucleophilic substitution, under the conditions of the reaction under consideration.



II I IX

IV, V III VI–VIII

IV $Ar = C_6H_5$; V $Ar = C_6H_4{-}NO_2\text{-}p$; VI $R^1 = CH_3$, $R^2 = C_6H_5$; VII $R^1R^2 = (CH_2{-}CH_2)_2$;

VIII $R^1R^2 = (CH_2{-}CH_2)_2CH_2$

The reaction of 2-ethoxy-3-phenoxazinone, obtained by refluxing the silver salt of I with ethyl iodide, with both arylamines and cycloalkylimines is accompanied by nucleophilic substitution of the ethoxy group to give 2-amino derivatives of 3-phenoxazinone (IV-VIII). Traces of the products of nucleophilic substitution of the hydrogen atom in the 7 position are detected only by chromatography.

The structures of 2-amino derivatives IV-VIII were confirmed from the disappearance of the signal of the 2-H proton in the PMR spectra of these compounds; this signal is found at 6.76 ppm in the spectrum of unsubstituted 3-phenoxazinone. Compounds VII-VIII are identical to the morpholino- and piperidino-3-phenoxazinones obtained directly from 3-phenoxazinone [3]. This confirms that replacement of the hydrogen atom in the 2 position of the quinone-imine portion of the molecule occurs by the direct action of the amine on 3-phenoxazinone.

It is interesting that cyclization due to condensation of the secondary amino group with the exocyclic oxygen atom occurs along with replacement of the ethoxy group in the 2 position in the reaction of 2-ethoxy-3-phenoxazinone with o-phenylenediamine; the product in this case is the previously described oxazinophenazine [10].

Thus the data on the reactivities of 2- and 7-substituted derivatives of 3-phenoxazinone in their reactions with amines indicate that not only replacement of a hydrogen atom but also displacement of groups that are inclined to undergo detachment in the form of an anion occur more readily in the electrophilic center of the quinoid ring than attack by the nucleophile on the 7 position in the benzo ring.

EXPERIMENTAL

The R_f values were determined on Silufol UV-254 plates in the following systems: chloroform for IV and chloroform—acetone (40:1) for V-VI.

2-Ethoxy-3-phenoxazinone (III). An aqueous solution of 1 g (6.0 mmole) of silver nitrate was added to the sodium salt of 2-hydroxy-3-phenoxazinone, obtained by dissolving 1 g (5.7 mmole) of I in 50 ml of 0.5 N NaOH solution, and the precipitated silver salt was re-

moved by filtration and dried. A mixture of 2 g (6.3 mmole) of the silver salt of I and 8 ml (0.3 mole) of ethyl iodide in 25 ml of alcohol was refluxed for 30 min, and the hot solution was filtered to remove the precipitated silver iodide. The precipitate that formed from the filtrate was removed by filtration, washed with alcohol, dried, and chromatographed with a column filled with activity III aluminum oxide in a benzene–acetone (3:1) system. The yellow fraction was collected, the solvent was removed by evaporation, and the residue was crystallized to give 0.5 g (88%) of a product with mp 211-212°C (from butanol). Found: C 69.3; H 4.6; N 5.9%. $C_{14}H_{11}NO_3$. Calculated: C 69.7; H 4.6; N 5.8%.

2-Anilino-3-phenoxazinone (IV). A 2.5 ml (0.25 mole) sample of aniline was added to a solution of 1 g (3.9 mmole) of II in 50 ml of alcohol, and the mixture was refluxed for 70 min. It was then cooled, and the precipitate was removed by filtration, washed with alcohol, dried, and chromatographed with a column filled with activity II aluminum oxide (elution with anhydrous chloroform). The brown fraction was collected, and the solvent was removed by evaporation to give 0.12 g of IV (Table 1).

2-(p-Nitroanilino)-3-phenoxazinone (V). A 0.5 g (3.6 mmole) sample of p-nitroaniline and 0.2 g of p-nitroaniline hydrochloride were added to a suspension of 0.22 g (0.9 mmole) of II in 20 ml of alcohol, and the mixture was refluxed for 6 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with alcohol to give 0.21 g of V (Table 1).

2-N-Methylanilino-3-phenoxazinone (VI). A total of 0.4 g of VI (Table 1) was obtained by refluxing 0.5 g (2.1 mmole) of III and 6 ml (0.056 mole) of N-methylaniline in 20 ml of alcohol for 7 h.

Compounds IV and V were similarly obtained from 2-ethoxy-3-phenoxazinone.

2-Morpholino-3-phenoxazinone (VII). A 3.5 ml (0.04 mole) sample of morpholine and 0.6 g of morpholine hydrochloride were added to a suspension of 0.5 g (2.1 mmole) of III in 20 ml of alcohol, and the mixture was refluxed for 17 h. The precipitate was removed by filtration, dried, and chromatographed with a column filled with activity II aluminum oxide (elution with anhydrous chloroform). The brown fraction was collected, and the solvent was removed by evaporation to give 0.48 g (70%) of VII.

2-Piperidino-3-phenoxazinone (VIII). This compound was similarly obtained in 58% yield by refluxing 0.2 g (0.91 mmole) of III in 1 ml of piperidine and 10 ml of alcohol.

Oxazinophenazine (IX). A 0.5 g (2.1 mmole) sample of III was suspended in 20 ml of alcohol, 0.5 g (4.6 mmole) of o-phenylenediamine was added, and the mixture was refluxed for 9 h. It was then cooled, and the precipitate was removed by filtration and crystallized from DMF to give 0.55 g (93%) of IX. Found: C 76.1; H 3.9; N 14.7%. $C_{18}H_{11}N_3O$. Calculated: C 75.7; H 3.9; N 14.7%.

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