RESEARCH ON THE CHEMISTRY OF PHENOXAZINES

VIII.* SYNTHESIS OF AMINO DERIVATIVES OF PHENOXAZINONES

I. Ya. Postovskii, K. I. Pashkevich, and G. B. Afanas'eva

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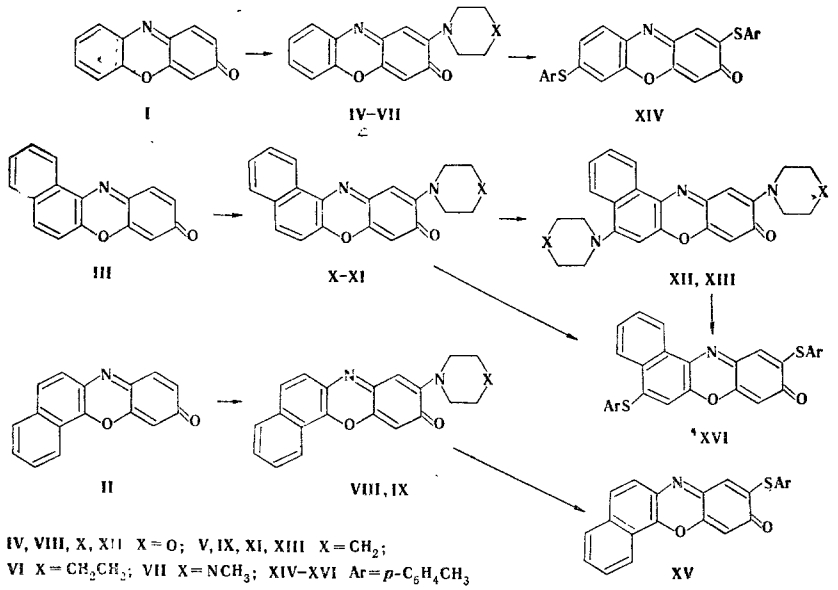
The reaction of 3-phenoxazinone, benzo[c]phenoxazin-3-one, and benzo[a]phenoxazin-9-one with piperidine and other similar amines leads to replacement of a hydrogen atom in the quinoid ring in the meta-position relative to the bridge nitrogen atom. Benzo[a]phenoxazin-9-one also forms 5,10-diamino derivatives. In all cases, the amine residue is displaced by thiophenol.

2-Amino-3-phenoxazinone has bacteriostatic action [2] and is the basis of antibiotics of the actinomycin class [3, 4]. No study of the physiological activity of aminophenoxazinones with a substituted amino group in the quinoid ring has been made up to now because of the lack of an acceptable method for the synthesis of these compounds.

The known method for the preparation of 2-amino-3-phenoxazinone is based on the oxidative condensation of o-aminophenol [5]. This method is not suitable for the preparation of N-substituted 2-amino derivatives of phenoxazinones. The possibility of the direct introduction of a thiophenol residue into the quinoid ring of phenoxazinones in the meta-position relative to the nitrogen atom (the 2-position in the case of 3-phenoxazinone) was shown in preceding papers [6, 7]. In the present research we have investigated



*See [1] communication VII.

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TABLE 1. Amino Derivatives of Phenoxazinones

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			λ_{max}, nm (log ε)	Yield, %
			C	H	N	C	H	N		
IV	210—211 (butanol – benzene) 4 : 1)	$C_{16}H_{14}N_2O_3$	68,0	5,1	10,5	68,1	5,0	10,0	426* (4,24) 440 (4,22)	43
V	184—186 (ethanol)	$C_{17}H_{16}N_2O_2$	72,9	5,8	10,0	72,9	5,7	10,0	427* (4,19) 443 (4,23)	53
VI	157—158 (isopropyl alcohol)	$C_{18}H_{18}N_2O_2$	73,6	6,2	9,8	73,4	6,2	9,5	— —	45
VII	186—187 (isopropyl alcohol)	$C_{17}H_{17}N_3O_2$	69,2	6,0	14,0	69,1	5,8	14,2	— —	42
VIII	235—236 (butanol)	$C_{20}H_{16}N_2O_3$	72,6	4,9	8,7	72,3	4,9	8,4	479 (4,47) 493* (4,45)	30
IX	238—239 (dimethylformamide)	$C_{21}H_{18}N_2O_2$	76,2	5,5	8,4	76,3	5,5	8,5	482* (4,47) 498 (4,49)	28
X	235—237 (isoamyl alcohol)	$C_{20}H_{16}N_2O_3$	71,9	5,1	8,1	72,3	4,9	8,4	491 (4,38)	40
XI	216—218 (isopropyl alcohol – benzene) (1 : 1)	$C_{21}H_{18}N_2O_2$	76,4	5,7	8,3	76,3	5,5	8,5	— —	45
XII	271—273 (dimethylformamide)	$C_{24}H_{23}N_3O_4$	69,0	5,5	10,2	69,1	5,5	10,0	525 (4,44)	25
XIII	260—262 (dimethylformamide)	$C_{26}H_{27}N_3O_2$	75,7	5,9	—	75,5	6,5	—	— —	40

*Shoulder.

the direct introduction of an amino group into the quinoid ring of 3-phenoxazinone (I), benzo[c]phenoxazin-3-one (II), and benzo[a]phenoxazin-9-one (III).

When secondary amines of the piperidine type are refluxed with I-III in benzene or alcohol, the amine residue enters the quinoid ring of the phenoxazinone molecule in the meta-position relative to the nitrogen atom to give monoamino derivatives IV-XI. In the case of III, diamino derivatives XII and XIII were also isolated (Table 1).

The introduction of an electron-donor substituent into the meta-position relative to the bridge nitrogen atom in the quinoid ring of phenoxazinones leads to a hypsochromic shift of the maximum of the long-wave band, while the introduction of the same substituent into the para-position relative to the nitrogen atom in the benzoid ring leads to a bathochromic shift of the maximum of this band [6, 7]. The maxima of the long-wave bands of the monoamino derivatives obtained in this study are shifted hypsochromically as compared with the maxima in the electronic spectra of the starting phenoxazinones (I-III); this attests to entry of the amine residues into the quinoid portion of the molecule.

To confirm the site of entry of the substituent we investigated the reaction of 3-phenoxazinone with ammonia. It was found that the known 2-amino-3-phenoxazinone [5] is formed when the reactants are heated in sealed tubes for a long time, i.e., the attack of the amine is actually directed to the quinoid ring in the meta-position relative to the nitrogen atom.

The amino group in the amino derivatives (IV-XII) of phenoxazinones is readily displaced by a thiocresol residue. Moreover, in the case of monoamino derivatives of 3-phenoxazinone and benzo[a]phenoxazino-9-one, in addition to displacement one observes entry of a second thiophenol molecule into the benzoid ring of I and III to give di(arylthio) derivatives XIV and XVI, which are identical to the compounds obtained in [6, 7]. Only displacement of the amine residue by thiophenol to give XV is observed for amino derivatives of benzo[c]phenoxazin-3-one, in which there is no electrophilic center in the benzoid ring (VIII and IX). The described reactions also confirm the entry of amines into the quinoid ring of I-III.

EXPERIMENTAL

The absorption spectra of $5 \cdot 10^{-4}$ M solutions of the compounds in chloroform were recorded with an SF-10 spectrometer. Column chromatography was carried out with activity II neutral aluminum oxide with elution with anhydrous chloroform.

2-Morpholino-3-phenoxazinone (IV). A 2-ml (20 mmole) sample of morpholine was added to 0.5 g (2.5 mmole) of 3-phenoxazinone in 10 ml of benzene, and the mixture was refluxed on a water bath for 4 h. It was then cooled, and the precipitated crystals were removed by filtration, washed with alcohol, and dried. The dry precipitate was dissolved in chloroform and chromatographed with a column. The first (red) fraction was collected, the solvent was removed by distillation, and the residue was recrystallized to give 0.5 g of amine IV (Table 1).

2-Piperidino- (V), 2-Hexamethyleneimino- (VI), and 2-(N-Methyl-piperazino)phenoxazin-3-ones (VII) and 2-Morpholino- (VIII) and 2-Piperidino- benzo[c]phenoxazin-3-ones (IX). These compounds were similarly obtained.

2-Amino-3-phenoxazinone. A 0.5-g (2.5 mmole) sample of 3-phenoxazinone was heated in 10 ml of alcohol saturated with ammonia in a sealed tube at 95-100° for 10 h. The solvent was then removed, and the residue was dissolved in chloroform and chromatographed. The yellow-orange fraction was collected, the solvent was removed by distillation, and the residue was recrystallized to give 0.1 g (18%) of 2-amino-3-phenoxazinone, which was identical to the compound obtained by independent synthesis via the method in [5]. The product had mp 249-250° (from alcohol).

10-Morpholinobenzo[a]phenoxazin-9-one (X). A 2-ml (20 mmole) sample of morpholine was added to a mixture of 25 ml of benzene and 0.8 g (3 mmole) of benzo[a]phenoxazin-9-one, and the mixture was refluxed on a water bath for 4 h. It was then cooled, and the precipitate was removed by filtration, washed, dried, and chromatographed with a column. The red fraction was collected, the solvent was removed by distillation, and the residue was recrystallized to give 0.3 g of amine X (Table 1).

5,10-Dimorpholinobenzo[a]phenoxazin-9-one (XII). A mixture of 0.8 g (3 mmole) of benzo[a]phenoxazin-9-one, 6 ml (60 mmole) of morpholine, and 10 ml of benzene was refluxed for 8 h. It was then cooled, and the resulting precipitate was removed by filtration, dried, and chromatographed with a column. The violet fraction was collected, the solvent was evaporated, with a column. The violet fraction was collected, the solvent was evaporated, and the residue was recrystallized to give 0.3 g of amine XII.

10-Piperidinobenzo[a]phenoxazin-9-one (XI) and 5,10-Dipiperidinobenzo[a]phenoxazin-9-one (XIII). These compounds were similarly obtained (see Table 1).

2,7-Di(tolylthio)phenoxazin-3-one (XIV). A 0.5-g (1.8 mmole) sample of 2-morpholino-3-phenoxazinone and 0.3 g (2.4 mole) of p-thiocresol was heated in 10 ml of alcohol with two drops of hydrochloric acid for 4 h on a water bath, after which another 0.1 g (0.8 mmole) of p-thiocresol was added, and the mixture was refluxed for 2 h. After this, 5 ml of 10% alcohol solution of ferric chloride was added, and the solvent was removed by distillation. The dry residue was dissolved in chloroform and chromatographed with a column. The first (red) fraction was collected, the solvent was evaporated, and the residue was recrystallized to give 0.3 g of dithio derivative XIV with mp 232-233° (from butanol). The product was identical to the 2,7-di(tolylthio)-3-phenoxazin-3-one obtained by direct reaction of p-thiocresol with 3-phenoxazinone.

The amine residue was similarly displaced by thiocresol from the other amino derivatives of 3-phenoxazinone, benzo[c]phenoxazin-3-one, and benzo[a]phenoxazin-9-one.

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