

PHENOXAZINE DERIVATIVES — PRODUCTS OF THE REACTION OF o-AMINOPHENOL
WITH CHALCONES

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The reaction of o-aminophenol with 4- and 4'-substituted chalcones and benzalacetones in methanol (with a tertiary amine as the catalyst), which leads to products of β addition of 2-aminophenoxazin-3-one to the C=C bond of an unsaturated ketone, was investigated. The activating role of the unsaturated ketone in the formation of a phenoxazine fragment was examined. The structures of the synthesized compounds were confirmed by IR, UV, PMR, and mass spectrometry.

Dinucleophiles of the o-phenylenediamine, o-thioaminophenol, and o-aminophenol type react with mesityl oxide [1-3] to give benzodiazepine, benzothiazepine, and benzoxazepine derivatives. It has also been reported [4-6] that the first two dinucleophiles also undergo reaction with aromatic α,β -unsaturated ketones; information regarding the participation of o-aminophenol in a similar reaction is not available in the literature, and we therefore set out in the present research to study the reaction of o-aminophenol with chalcones.

The methods previously described in [1-6] constituted the foundation of our experimentation; however, most of them were found to be ineffective. Thus when we heated the chalcone with o-aminophenol in a benzene-sulfoxide solution (the conditions used for mesityl oxide [3]), we did not obtain the desired product; the starting reagents were recovered in all the experiments. An experiment under the conditions described in [5] in the case of the reaction of o-aminothiophenol with chalcones, viz., in the case of refluxing with a Dean-Stark adapter of equimolar amounts of the starting components in toluene solution, was also unsuccessful.

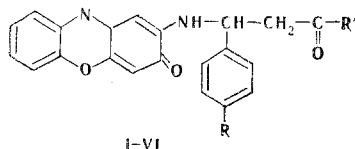
The reaction of o-aminophenol with chalcones was observed under the conditions of our proposed [6] method for the synthesis of 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepines (with methanol as the solvent and a tertiary amine as the catalyst); powdery red products (I-VI) were obtained in low yields (10-17%), and a certain amount of the starting compound was recovered from the reaction. The reaction proceeded absolutely similarly both in the case of 4- and 4'-substituted chalcones, as well as in the case of benzylideneacetone.

Compounds I-VI are characterized by high melting points, low solubilities in organic solvents, deep color (λ_{\max} of the long-wave absorption ranged from 432-435 nm), and by the presence in the IR spectra of several absorption maxima at 1600-1700 cm^{-1} , as well as a $\nu_{\text{N-H}}$ band at 3332-3382 cm^{-1} (Table 1). The following signals are observed in the PMR spectra [trifluoroacetic acid (TFA)-benzene (5:1), 80 MHz] of I: 2.97 (q, CH_2), 5.20 (s, CH), 5.79 (s, aromatic CH), 6.53-7.60 (m, aromatic CH), and 8.38 ppm (s, NH) with an intensity ratio of 2:1:1:15:1. Peaks with larger m/e values than for the expected diarylbenzoxazepines are observed in the mass spectra of I, III, and IV. The results of elementary analysis for the nitrogen content show that 2 moles of o-aminophenol reacted with 1 mole of chalcone. All of the information stated above distinguishes the reaction products obtained from the desired 2,4-diaryl-2,3-dihydro-1,5-benzoxazepines.

Usual pathways for the reactions of o-phenylenediamine with ketones that lead to the formation of phenazine derivatives have been reported [7, 8]; β -diketones and methyl isopropyl ketone give 2,3-diaminophenazine monoazomethines [7], while benzylidene derivatives of acetone and cyclohexanone give 2,3-dihydroimidazo[4,5-b]phenazines [8]. The intermediate oxidation of o-phenylenediamine to diaminophenazine was noted in both studies.

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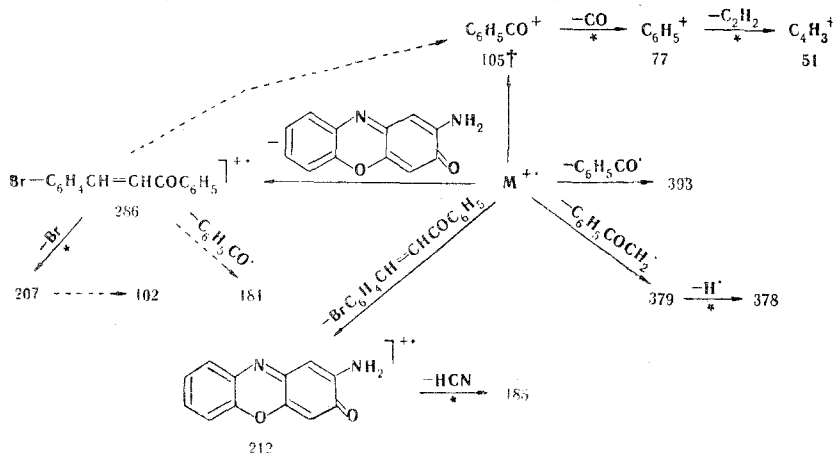
The occurrence of a similar oxidative process that leads to the formation of phenoxazine derivatives can also be proposed for the investigated reaction. Compounds I-VI obtained in this study can then be identified as products of the addition of 2-aminophenoxazin-3-one to unsaturated ketones.



I R=H, R'=C₆H₅; II R=OCH₃, R'=C₆H₅; III R=H, R'=p-CH₃OC₆H₄ IV R=Br, R'=C₆H₅; V R=H, R'=p-NO₂C₆H₄ VI R=H, R'=CH₃

The phenoxazine fragment is responsible for the red color of I-VI (2-aminophenoxazin-3-one itself absorbs at 430-434 nm [9]), while saturation of the chalcone fragment during the formation of these compounds clears up the question of the effect of R and R' on the long-wave part of the absorption spectra. The presence in the molecule of two nonequivalent C=O and C=N groups and a strongly polarized aromatic ring is responsible for the appearance of a large number of bands at 1600-1700 cm⁻¹. The PMR spectra of I are also in good agreement with the proposed structure [when excess trifluoroacetic acid (TFA) is present, I may undergo substantial protonation, which should be reflected in the chemical shifts of the individual protons but not in their multiplicity].

The mass spectra confirm the structure proposed for I-VI (Table 2). In the case of IV one can trace the following pattern of the fragmentation (the mass numbers of the ions that contain bromine are presented for the ⁷⁹Br isotope):



Under the influence of electron impact IV undergoes fragmentation via several pathways: elimination of PhCO and PhCOCH₂ radicals leads to ions 393 and 379, respectively; splitting out of the PhCH=CHCOPh chalcone molecule gives a rearranged 2-aminophenoxazin-3-one ion radical (212), while ejection of a phenoxazine molecule leads to a chalcone ion radical (286). The 207, 181, 179, 102, and, possibly, some of the 105, 66, and 51 ions are formed during the subsequent fragmentation of the chalcone quasi-molecular ion [10], while fragmentation of the 2-aminophenoxazin-3-one quasi-molecular ion gives the 185, 184, and 156 ions [9, 11]. The PhCO⁺, Ph⁺, and -C₄H₃⁺ ions constitute 40% of the total ion current. The high stability of these ions was previously noted during a mass-spectrometric study of chalcones [10], as well as for a number of other compounds that contain a benzoyl group [12].

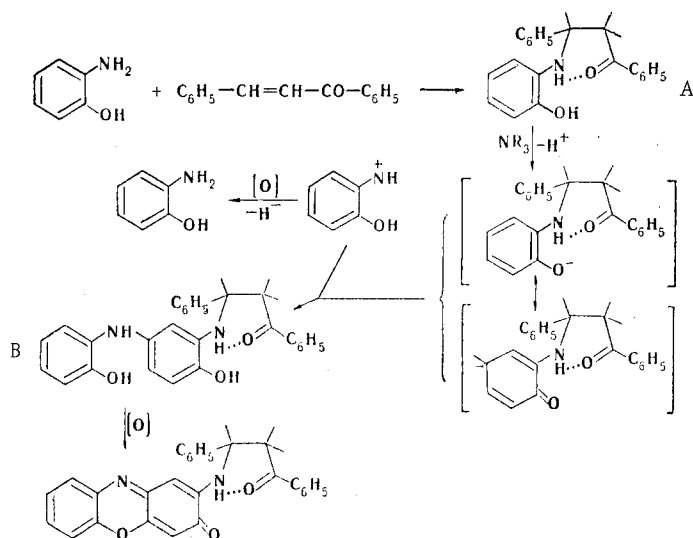
While, in our opinion, there is no doubt whatsoever regarding the proposed structures of I-VI, the problem of the pathways involved in their formation is rather complex. The ability of o-aminophenol to undergo oxidation to 2-aminophenoxazin-3-one has long been known [13], and the oxidation conditions have been double-checked more than once. The oxidation of aminophenol by means of benzoquinone [14] should probably be assumed to be one of the most feasible mechanisms for this process. However, there are still many unclear fea-

*Metastable transitions.

†Here and subsequently in the text, the numbers that characterize the ions are the mass-to-charge ratios.

tures in the details of the mechanism of this reaction. The only thing that has been firmly established is that the intermediate in the oxidation of aminophenol is o-iminoquinone [15].

In our study we addressed ourselves to the fact that the formation of 2-aminophenoxazin-3-one is not observed under the conditions of a blank experiment (in the absence of a chalcone). Moreover, an experiment showed that 2-aminophenoxazin-3-one itself does not react with the chalcone under the same conditions. Hence it follows in all likelihood that this heterocyclic ketone is not a direct reaction intermediate. However, it is just as clear that the chalcone initiates the formation of the phenoxazine ring. If one chooses the point of view regarding a hydride mechanism for the oxidation of aniline [16], this process can hypothetically be represented by the following scheme:



In this case the activating role of the chalcone is explained by stabilization of intermediate B by an intramolecular hydrogen bond. This factor favors an increase in the electron density on the adjacent aniline ring and consequently facilitates the subsequent electrophilic processes, and this accelerates the oxidation of intermediate B substantially.

The chemical behavior of 4'-nitrochalcone constitutes evidence in favor of this assumption. The nitro group in this compound substantially lowers the electron density on the oxygen atom of the carbonyl group, which should weaken the intramolecular hydrogen bond (IHB) in intermediate B and thereby slows down its oxidation. In fact, the reaction of o-aminophenol with this chalcone proceeds slowly, and the formation of V in 10% yield requires no less than 10 days. Intermediate B cannot be isolated. However, to a first approximation one can form a judgment regarding the character of the hydrogen bond in it from the IR spectra of the final products I-VI. It is apparent from Table 1 that pronounced weakening of the IHB is characteristic precisely for adduct V.

The question as to the role of the oxidizing agent still remains unanswered. It is known that o-aminophenol undergoes partial oxidation during storage; the process is accelerated appreciably in alcohol solutions. In addition, the reactions of the chalcone with both reprecipitated aminophenol and with the crude compound give approximately equal yields. The presence of reducing agents (Na_2S , $\text{Na}_2\text{S}_2\text{O}_3$, and $\text{Na}_2\text{S}_2\text{O}_4$), as well as the presence of a mild oxidizing agent ($\text{K}_2\text{S}_2\text{O}_5$), has no substantial effect on the reaction rate and the yields of products. Heating the starting compounds in a sealed ampul or in a nitrogen atmosphere does not give the desired product; on the other hand, passage of oxygen promotes the reaction and increases the yield of I. Thus one may arrive at the conclusion that air oxygen acts as the oxidizing agent in this reaction. The rate of its diffusion into the solution also determines the rate of the process to a significant extent. Thus up to 30% of I is formed when the reaction mixture is allowed to stand for a long time (up to 7-10 days) at room temperature, while carrying out the reaction with heating lowers the yield of this product. For the same reason, varying the ratio of the starting components has little effect on the reaction rate. The ionic character of the oxidative process is emphasized by the fact that the polarity of the medium plays an important role in it: Replacement of methanol by aromatic solvents brings the formation of I-VI to a complete halt.

TABLE 1. 2-[N-(1,3-Diaryl-3-oxopropyl)amino]phenoxazin-3-ones

Compound	mp, °C	UV spectrum (in toluene), λ_{\max} , nm ($\epsilon \cdot 10^{-3}$)	IR spectrum (in KBr), ν , cm ⁻¹				N found, %	Empirical formula	N cal- cu- lated, %	Yield, %*
			C=N	C=O†	C=O†	N-H				
I	262—264	434 (28,4)	1616	1639	1683	3332	6,82	C ₂₇ H ₂₀ N ₂ O ₃	6,66	15
II	240—241	433 (28,9)	1617	1643	1684	3339	6,10	C ₂₈ H ₂₂ N ₂ O ₄	6,21	12
III	239—240	435 (26,8)	1607	1656	1675	3338	6,00	C ₂₈ H ₂₂ N ₂ O ₄	6,21	15
IV	264—266	432 (30,6)	1614	1639	1684	3333	5,70	C ₂₇ H ₁₉ BrN ₂ O ₃	5,61	10
V	272—273	434 (29,8)	1595	1668	1691	3382	9,15	C ₂₇ H ₁₉ N ₃ O ₅	9,00	10
VI	242—243	433 (22,0)	1617	1640	1710	3336	8,25	C ₂₂ H ₁₈ N ₂ O ₃	8,16	17

*The yields of the compounds obtained by method A are presented. †The C=O and C=O' bonds characterize the carbonyl groups of the heteroring and the side chain, respectively.

TABLE 2. Mass Spectra of I, III, and IV

Com- pound	m/e values (peak intensities, %*)
I	420 (8), 300 (16), 299 (9), 212 (6), 208 (6), 207 (6), 197 (7), 185 (7), 169 (7), 156 (7), 140 (7), 131 (13), 130 (5), 105 (100), 104 (12), 103 (20), 102 (9), 89 (6), 78 (17), 77 (83), 76 (13), 52 (20), 51 (10)
III	450 (2), 315 (9), 314 (9), 302 (15), 301 (14), 300 (9), 239 (45), 238 (27), 223 (13), 212 (57), 210 (9), 207 (10), 185 (34), 184 (21), 179 (6), 178 (5), 156 (6), 144 (8), 135 (100), 131 (12), 107 (8), 103 (17), 102 (7), 78 (5), 77 (20), 64 (7), 63 (6), 51 (10), 50 (7)
IV	500 (1), 498 (1), 288 (9), 287 (5), 286 (9), 213 (5), 212 (19), 211 (5), 209 (5), 207 (18), 185 (13), 184 (9), 181 (9), 179 (11), 178 (8), 130 (9), 105 (100), 103 (5), 102 (35), 101 (8), 89 (8), 78 (9), 77 (64), 76 (18), 75 (12), 63 (8), 52 (9), 51 (30), 50 (15)

*The peaks of the molecular ions and the ions with intensities $\geq 5\%$ are presented.

In conclusion, it should be noted that I-VI are unstable in acidic media and are readily cleaved to give the starting unsaturated ketones and 2-aminophenoxazin-3-one.

EXPERIMENTAL

The IR spectra of KBr pellets of I-VI were measured with a UR-20 spectrometer. The UV spectra of solutions of the compounds in toluene ($1 \cdot 10^{-5}$ mole/liter) were recorded with a Specord UV-vis spectrophotometer. The PMR spectrum of I in trifluoroacetic acid (TFA)-benzene solutions (5:1) was measured with a Bruker spectrometer with an operating frequency of 80 MHz and tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT CH-6 spectrometer with direct introduction of the samples into the ion source; the ionization-chamber temperature was 180°C, the ionizing voltage was 70 eV, and the emission current was 100 μ A. The temperature to which the samples were heated ranged from 180 to 200°C, depending on their volatilities.

2-[N-(1,3-Diaryl-3-oxopropyl)amino]phenoxazin-3-one (I). A) Equimolecular amounts (0.01 mole) of the chalcone (2.08 g) and o-aminophenol (1.09 g) were dissolved in 25 ml of methanol, 0.5 ml of triethylamine was added, and the mixture was heated for 3-3.5 h and allowed to stand at 20°C for 10-12 h. The resulting precipitate was crystallized from toluene to give 0.63 g (15%) of a product with mp 262-264°C.

Compounds II-IV and VI were similarly obtained. In the synthesis of V the mixture was allowed to stand for 10 days.

B) The procedure was the same as in experiment A, except that the molar ratio of the aminophenol and chalcone was 2:1. The yield was 1.0 g (24%).

C) The procedure was the same as in experiment B, except that a stream of pure oxygen was passed continuously into the solution. The yield was 1.35 g (32%).

Acid Cleavage. A 0.1-g sample of I was dissolved in 10 ml of methanol and 4 ml of 10% hydrochloric acid. The solution took on an intense violet color. It was refluxed for ~10 h, after which the solvent was removed by distillation, and the residue was chromatographed with a column filled with aluminum oxide (elution with chloroform). As a result, we isolated the chalcone and 2-aminophenoxazin-3-one (identified from their melting points and IR and UV spectra).

2-Aminophenoxazin-3-one. This compound was obtained by the method in [14]. Its reaction with chalcone was studied under the conditions of experiment A; the starting components were recovered unchanged.

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