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SYNTHESIS AND AUTOOXIDATIVE TRANSFORMATION OF 2-(2-AMINOPHENYL)-4-HYDROXY-3-PHENYL-1-ISOQUINOLONE

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UDC 547.833.7.07:542.943

2-(2-Aminophenyl)-4-hydroxy-3-phenyl-1-isoquinolone was unexpectedly obtained in the reaction of 3-(α-bromobenzyl)-3-bromophthalide with o-phenylenediamine. The isoquinolone in chloroform undergoes autooxidation by air oxygen to give 2-(2-aminophenyl)-3-hydroperoxy-3-phenyl-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline, which is subsequently converted to N-(2-benzamidophenyl)phthalimide. A mechanism is proposed for the rearrangement of the hydroperoxide.

It is known [1-3] that 3-substituted 3-halophthalides react with aromatic amines to give two series of derivatives, viz., 3-aminophthalides and 3-hydroxyisoindolinones. The aim of the present research was to investigate the reaction of 3-(α-bromobenzyl)-3-bromophthalide (I) with o-phenylenediamine. It has been shown [4] that the reactions of phthalide I with alkylamines and aniline lead to N,N'-disubstituted 2-α-aminophenylacetylbenzamides. However, it was established by a spectroscopic reinvestigation that these compounds have the ring structure of 3-α-aminobenzyl-3-hydroxyisoindolinones [5].

It might be assumed that primary nucleophilic attack on the phthalide I molecule by o-phenylenediamine would take place at the C=O group and that subsequent cyclization would lead to ten-membered heteroring II or, which is more likely, to its isomers III and IV. The possible products of this reaction (II-V) can undergo interisomerization due to intramolecular reversible reactions involving nucleophilic addition of the N–H group to the C=O bond. A number of products with different structures can be formed as a result of the less probable primary nucleophilic attack at the C–Br bonds in the I molecule.

It turned out unexpectedly that 2-(2-aminophenyl)-4-hydroxy-3-phenyl-1-isoquinolone (VI) is formed in good yield when the reaction between equimolar amounts of phthalide I and o-phenylenediamine is carried out in refluxing dioxane in the presence of triethylamine.

Isoquinolone VI is soluble in both acids and alkilis. An NH band (3395 cm^{-1}), a broad OH band (3230 cm^{-1}), and bands at 1654, 1621, and 1578 cm^{-1} are observed in the IR spectrum of crystalline VI (Fig. 1); this is in good agreement with the literature data [6-8] for 2-substituted 4-hydroxy-3-phenyl(or alkyl)-1-isoquinolones.

The problem of the assignment of these bands is not clear-cut [8], since the band at 1578 cm^{-1} is the most intense band in the spectrum of the crystalline substance (see Fig. 1). Such a low frequency does not make it possible to assign this band to the absorption of the C=O group of the isoquinolone. The presence of a very wide band at 3230 cm^{-1} provides a basis for the assumption that strong C=O...H–O– intermolecular hydrogen bonds exist in the crystalline state and that this in turn may lead to redistribution of the electron density in the

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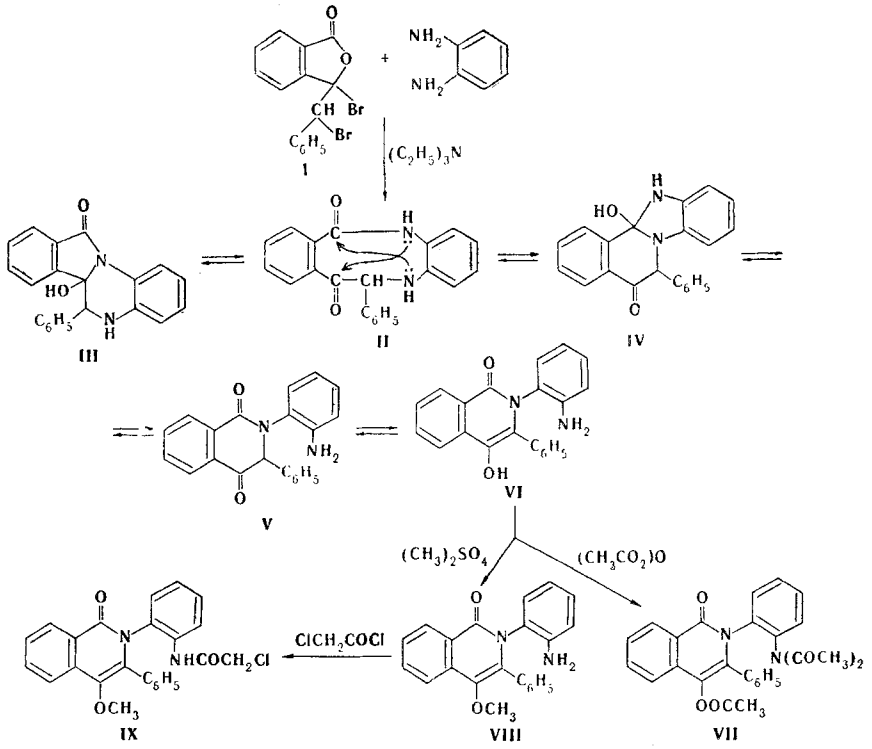
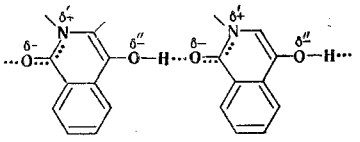


isoquinoline system and to the formation of linear associates with a strongly polarized structure:



The bands at 1654 and 1621 cm^{-1} corresponding to this structure can be assigned to the absorption of the $C^{\cdot\cdot}\!=\!N^{+}$ and C=C bonds, while the band at 1578 cm^{-1} can be assigned to the absorption of the $C^{\cdot\cdot}\!=\!O^{-}$ group.

The IR spectrum of a solution of **isoquinolone** VI in dioxane differs markedly from the spectrum of the crystalline compound (see Fig. 1) and constitutes evidence for a shift of the tautomeric equilibrium to favor dioxo form V, which is in agreement with the data in [8]. The band at 1713 cm^{-1} is related to the absorption of the keto group, while the band at 1670 cm^{-1} is related to the absorption of the lactam C=O group.

In order to confirm the structure of **isoquinolone** VI we synthesized a number of its **derivatives. In the case** of exhaustive acetylation with refluxing acetic anhydride we obtained triacetyl derivative VII, in the IR spectrum of which we observed absorption bands of all four C=O groups; the UV spectrum of this product is in agreement with the data in [8] for 4-hydroxy-3-phenyl-1-isoquinolone derivatives. The structures of O-methyl derivative VIII and its N-chloroacetyl derivative IX were confirmed by their PMR, IR, and UV spectra.

The recrystallization of isoquinolone VI is realized in low yields and is accompanied by contamination. When a solution of VI in chloroform is stored for 24 h at 20°C with access to the air, a substance with mp 204-205°C is isolated from the solution. Absorption bands at 1789 (A = 0.63 practical units),* 1726 (7.27), 1685 (3.25), 1598, and 1522 cm^{-1} are observed in the IR spectrum of a solution in dioxane. The presence of bands at 1789 and 1726 cm^{-1} and their intensity ratio (~1:11) made it possible to assume **that this compound** is a phthalimide derivative (see [9]), while the bands at 1685 (3.40 practical units, amide I), 1522 **(amide II),**

*The integral intensities A calculated in practical units of measurement, viz., 10^{4} **liters·mole^{-1}·cm^{-2} (ln),** are presented in parentheses.

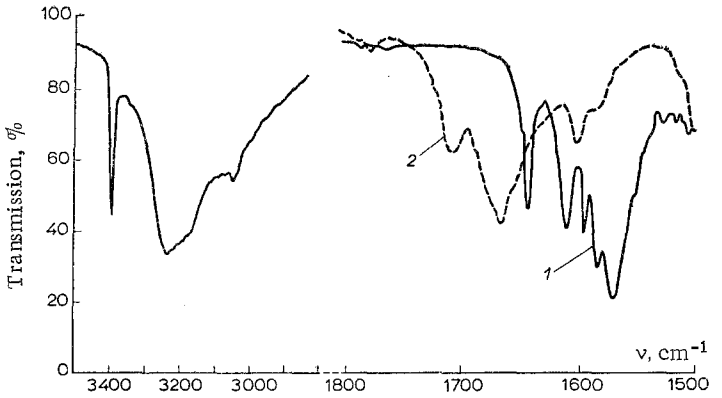


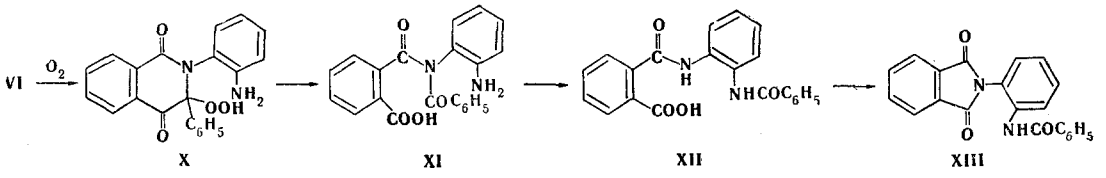
Fig. 1. IR spectrum of 2-(2-aminophenyl)-4-hydroxy-3-phenyl-1-isoquinolone: 1) in Nujol; 2) in dioxane.

and 3345 cm^{-1} (NH) made it possible to refine this assumption down to the N-(2-benzamidophenyl)phthalimide structure (XIII). The XIII structure was confirmed definitively by alternative synthesis: The substance obtained by benzoylation of N-(2-aminophenyl)phthalimide proved to be identical to XIII.

To ascertain the mechanism of such a profound transformation of isoquinolone VI under mild conditions we made attempts to isolate the intermediates. In the case of briefer storage of the solution of isoquinolone VI in chloroform we isolated 2-(2-aminophenyl)-3-hydroperoxy-3-phenyl-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline (X). A similar reaction involving autooxidation of 2,3-dialkyl-4-hydroxy-1-isoquinolones was described in [10].

Bands of a lactam carbonyl group at 1667 cm^{-1} (3.46 practical units) and 1712 cm^{-1} (2.10 practical units) are observed in the IR spectrum of a solution of hydroperoxide X in dioxane; this is in agreement with the data in [10]. The X structure was also confirmed by iodometric determination of the peroxide oxygen.

We then demonstrated that hydroperoxide X in chloroform at room temperature slowly undergoes conversion to phthalimide XIII. The following scheme for the autooxidation of isoquinolone VI to phthalimide XIII can be proposed:



We were unable to isolate intermediates XI and XII; however, an analog of the X → XI transformation, viz., cleavage of the 4-hydroxy-1-isoquinolone ring through the intermediate formation of the hydroperoxide, was described in [11] for the more complex system of a berberine derivative. This is followed by the well-known [12, 13] migration of an acyl group (XI → XII) and cyclization to a phthalimide.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in Nujol and solutions in dioxane [2.5-5)•10^{-2} mole/liter] were recorded with a Specord 75-IR spectrometer. The integral intensities (A) of the bands were calculated by the Wilson-Wells method with corrections for the Ramsay wing [14]. The UV spectra of solutions of the compounds in ethanol ($5•10^{-5}$ mole/liter) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were obtained with a Bruker WH-90/DS spectrometer (90 MHz) with hexamethyldisiloxane as the internal standard. The individuality of the compounds was confirmed by thin-layer chromatography (TLC) on Silufol UV-254 plates.

2-(2-Aminophenyl)-4-hydroxy-3-phenyl-1-isoquinolone (VI). A solution of 7.64 g (20 mmole) of phthalide I, 2.16 g (20 mmole) of o-phenylenediamine, and 5.6 ml (40 mmole) of tri-

ethylamine in 50 ml of dioxane was refluxed for 1 h, after which it was diluted with 300 ml of water, and the precipitate was separated and suspended in 25 ml of ethanol. The suspension was heated to the boiling point, and the solid material was again separated and washed with ethanol to give 4.5 g (69%) of isoquinolone VI with mp 241°C (dec.). The IR spectrum is presented in Fig. 1. UV spectrum, λ_{max} (log ε): 209 (4.75), 233 (4.45), 303 (4.03), and 350 nm (3.68). Found: C 76.0; H 4.9; N 8.6%. $C_{21}H_{16}N_2O_2$. Calculated: C 76.8; H 4.9; N 8.5%.

4-Acetoxy-2-(2-N,N-diacetylaminophenyl)-3-phenyl-1-isoquinolone (VII). A solution of 0.5 g of isoquinolone VI in 10 ml of acetic anhydride was refluxed for 3 h, after which the acetic anhydride was decomposed with water, and the residue was recrystallized from 5 ml of ethanol to give 0.2 g (29%) of triacetyl derivative VII with mp 217-218°C. IR spectrum (Nujol): 1774 (CO–O); 1717 and 1692 (CO–N–CO); 1665 (isoquinolone CO); 1626 (C=C); 1606, 1595 cm^{-1}. UV spectrum, λ_{max} (log ε): 210 (4.76), 231 (4.50), 296 (4.07), and 333 nm (3.73). Found: C 71.1; H 4.8; N 5.9%. $C_{27}H_{22}N_2O_5$. Calculated: C 71.4; H 4.9; N 6.2%.

2-(2-Aminophenyl)-4-methoxy-3-phenyl-1-isoquinolone (VIII). A 2-ml sample of dimethyl sulfate was added in small portions with vigorous stirring to a solution of 1 g of isoquinolone VI in 100 ml of a 10% aqueous solution of potassium hydroxide, after which stirring was continued for 5 h. After 24 h, the precipitate was separated, washed with water, and recrystallized from 35 ml of ethanol to give 0.27 g (26%) of methoxy derivative VIII with mp 256-259°C. IR spectrum in Nujol: 3450, 3354, 3320, 3212 (N–H); 1654, 1636 (C=O); 1618 (C=C); 1604, 1590 cm^{-1}; in dioxane: 1665, 1658 (shoulder, C=O); 1620 (C=C); 1608, 1504 cm^{-1}. UV spectrum, λ_{max} (log ε): 210 (4.74), 230 (4.48), 300 (4.18), and 342 nm (3.83). PMR spectrum ($CDCl_3$): 3.42 (s, 3H, OCH_3), 3.80 (s, 2H, NH_2), 6.43-7.96 (m, 12H, aromatic protons, except for 8-H), and 8.54 ppm (q, 1H, 8-H). Found: C 77.2; H 5.5; N 8.3%. $C_{22}H_{18}N_2O_2$. Calculated: C 77.2; H 5.3; N 8.2%.

4-Methoxy-3-phenyl-2-(2-chloroacetamidophenyl)-1-isoquinolone (IX). A 0.5-mole sample of chloroacetyl chloride was added to a solution of 0.2 g of methoxy derivative VIII in 3 ml of dioxane, and the mixture was allowed to stand at room temperature. After 24 h, the mixture was diluted with water, and the precipitate was separated and recrystallized from ethanol to give 0.13 g (56%) of chloroacetyl derivative IX with mp 173-174.5°C. IR spectrum in dioxane: 1694 (amide C=O); 1657 (isoquinolone C=O); 1618 (C=C); 1600, 1585, 1558, 1518 cm^{-1} (amide II). UV spectrum, λ_{max} (log ε): 212 (4.75), 234 (4.55), 300 (4.13), and 340 nm (3.83). Found: C 68.3; H 4.6; Cl 9.0; N 6.6%. $C_{24}H_{19}ClN_2O_3$. Calculated. C 68.8; H 4.6; Cl 8.5; N 6.7%.

2-(2-Aminophenyl)-3-hydroperoxy-3-phenyl-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline (X) and N-(2-Benzaminophenyl)phthalmide (XIII). A) Air was blown through a suspension of 0.5 mole of isoquinolone VI in 20 ml of chloroform for 2 h, during which the solution was evaporated to a volume of ~8 ml. After 24 h, 0.28 g (51%) of hydroperoxide X, with mp 150-154°C (dec.), was separtaed. IR spectrum in Nujol: 3354, 3295, 3054, 2584, 1695 (ketone C=O); 1665 (lactam C=O); 1608, 1594, 1568 cm^{-1}. Found: C 70.4; H 4.5; N 7.8%. $C_{21}H_{16}N_2O_4$. Calculated: C 70.0; H 4.5; N 7.8%. The filtrate was evaporated to give 0.1 g (19%) of phthalimide XIII with mp 198-201°C. Crystallization from benzene gave a product with mp 204-205°C. IR spectrum in Nujol: 3345 (N–H); 1782, 1756, 1715 (phthalimide C=O); 1678 (amide C=O); 1600, 1592, 1579, 1514 cm^{-1} (amide II). Found: C 73.2; H 4.3; N 8.1%. $C_{21}H_{14}N_2O_3$. Calculated: C 73.2; H 4.7; N 8.1%.

B) A suspension of 1 g of isoquinolone VI in 40 ml of chloroform was refluxed for 10 min, after which it was cooled and allowed to stand at 20°C. The precipitated isoquinolone gradually dissolved, and hydroperoxide X began to precipitate. After 2, 4, and 6 days, the precipitates were separated and combined to give 0.5 g (45%) of hydroperoxide X with mp 150°C (dec.). The filtrate was evaporated *in vacuo* to give 0.25 g (24%) of phthalimide XIII with mp 200-203°C. Recrystallization from benzene gave a product with mp 204-205°C. Only phthalimide XIII was obtained when a suspension of the isoquinolone in chloroform was allowed to stand in an open vessel at room temperature for 10 days.

N-(2-Benzaminophenyl)phthalimide (XIII). A solution of 0.24 g of N-(2-aminophenyl)phthalimide [15], 0.12 ml of benzoyl chloride, and 0.14 ml of triethylamine in 4 ml of dioxane was heated at 100°C for 20 min. The solution was then cooled and diluted with 30 ml of water, and the precipitate was separated and recrystallized from ethanol and repeatedly from benzene to give 0.19 g (54%) of phthalimide XIII with mp 203-204°C. The identical character of this product and the product obtained in the preceding experiment was proved by a mixed-melting-point determination and from the IR spectra.

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ELECTROPHILIC SUBSTITUTION IN N-ARYL-2-PYRAZOLINES.

2.* REACTIONS WITH ALDEHYDES

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UDC 547.778

Leuco compounds of the triphenylmethane series were obtained by the reaction of 1,3-diphenyl-, 3-methyl-1,5-diphenyl-, 1,3,5-triphenyl-, and 1,5-diphenyl-3-styryl-2-pyrazolines with aromatic and heterocyclic aldehydes. The center of electrophilic attack is the para position of the aromatic ring in the 1 position of the heteroring.

It is known [1, 2] that compounds of the 2-pyrazoline group can react with benzaldehyde at high temperatures (~200°C) and in an inert atmosphere to give 4-benzylidene derivatives. It is characteristic that this phenomenon has been observed for compounds that do not contain a substituent in the 1 position of the heteroring. However, precisely pyrazoline systems of this type are devoid of a practically important property, viz., clearly expressed fluorescence [3]. It therefore seemed of interest to study the possibilities of the application of this reaction in a group of 1,3,5-triaryl-2-pyrazolines.

In the present research we selected the quite accessible 1,3,5-triphenyl-2-pyrazoline as the principal subject of our investigation. Attempts to carry out the reaction of this compound with benzaldehyde by the method in [2] (by refluxing in a medium of the pure aldehyde in an inert atmosphere) or under other conditions, viz., by heating a similar solution in sealed ampuls and by carrying out the reaction in various solvents [methanol, ethylene glycol, benzene, xylene, dioxane, and dimethylformamide (DMF)] in the absence and in the presence of catalysts with acidic (HCl, $ZnCl_2$, $AlCl_3$, and concentrated H_2SO_4) and basic (triethylamine, pyridine, and 40% NaOH) character, did not give positive results. The development of a blue-green coloration and its uniform deepening, which is complete in 1-1.5 h, are observed only when dioxane solutions are refluxed in the presence of $HClO_4$. The IR and UV spectra of the compound obtained constitute evidence for retention of the pyrazoline ring; this is also con-

*See [9] for our previous communication.

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