RESEARCH ON HETEROCYCLIC QUINONES. XXX.* ISOQUINOLINEQUINONES

Yu. S. Tsizin and B. V. Lopatin

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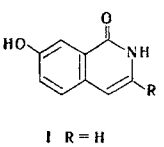
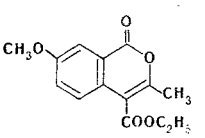
7-Hydroxy-1-isoquinolones, 3-methyl-7-hydroxyisoquinoline, and 6-hydroxyisoquinoline were synthesized, and their reactions, as well as the reaction of 7-methoxyisoquinoline-5,8-quinone, with amines were studied. The problem of the transmission of the mesomeric and inductive effects of the quinone carbonyl groups through the heteroring and the increase in the electrophilicities of the quinones upon chelate formation are discussed.

The oxidative amination of 7-hydroxyisoquinoline leads to 3,5-bis(dialkylamino)isoquinoline-7,8-quinones [2]. Amination at 3-C is not characteristic for isoquinolines but finds its explanation within the framework of concepts regarding the transmission of the mesomeric and inductive effects of the quinone carbonyl group through the heteroring [2,3]. Continuing our study of this phenomenon, we carried out the oxidative amination of 7-hydroxy-1-isoquinolones I and II. 7-Hydroxy-1-isoquinolone I was obtained by fusion of 7-hydroxyisoquinoline with potassium hydroxide. We used 4-methoxyhomophthalic acid, synthesized by the recently described method of arylation of acetoacetic ester with 2-bromo-5-methoxybenzoic acid and subsequent saponification and acid cleavage [4], for the synthesis of 3-methyl-7-hydroxy-1-isoquinolone (II). Ethyl 3-methyl-7-methoxyisocoumarin-4-carboxylate (III), the structure of which was confirmed by the results of elementary analysis and the IR and PMR spectroscopic data, as well as by alkaline cleavage, was isolated as a side product in 15% yield in the arylation reaction. 4-Methoxyhomophthalic acid was converted by a known method [5,6] to 3-methyl-7-methoxy-1-isoquinolone, which was demethylated to hydroxyisoquinolone II by refluxing in 48% HBr.

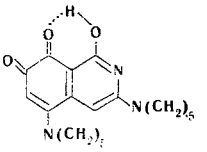
The oxidation of I with oxygen in the presence of the Cu^{2+}-piperidine complex leads to 1-hydroxy-3,5-dipiperidinoisoquinoline-7,8-quinone (IV), i.e., both the quinone ring and the heteroring are aminated. The reaction goes to completion only in the presence of an equivalent amount of copper salt because of tying up of the salt in a chelate complex of the V type. Quinone IV exists both in solution and in the solid state in the hydroxy form, which is stabilized by a strong intramolecular hydrogen bond, the presence of which is confirmed by spectroscopic data (in its PMR spectrum a broad singlet of a hydroxyl proton in found at very weak field at 13.7 ppm).



I R = H
II R = CH_3



III



IV

A larger amount of oxygen (~2.8 moles, see [3]) is absorbed in the oxidation of hydroxyisoquinolone II, and a quinone identical to IV is formed. According to the results of thin-layer chromatography (TLC), no other quinones are present in the reaction mixture. Thus in addition to oxidation and amination at 5-C, the methyl group is replaced by a piperidine residue; this is characteristic for quinones [7] and especially for quinazolinequinones [3]. In analogy with [3], it can be assumed that activation of the methyl group is achieved through the formation of an electron-acceptor pseudoaromatic ring that develops during chelate bonding of the copper by intermediate quinone V. It seemed of interest to ascertain whether the methyl group would be replaced when the reaction product is incapable of forming this sort of chelate. For this, we oxidized 3-methyl-7-hydroxyisoquinoline (VI), which was obtained from 3-methyl-7-methoxy-1-isoquinolone in three steps.

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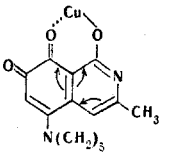
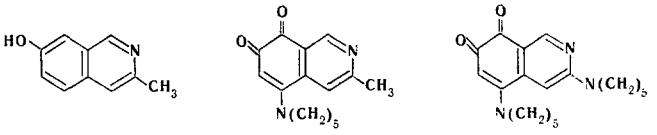


V

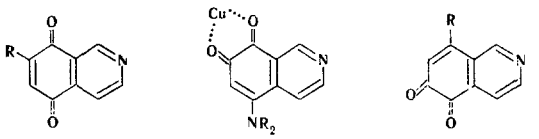
The oxidation of VI in the presence of piperidine proceeds with a catalytic amount of copper salt, during which, according to the TLC data, a mixture of approximately equal amounts of three compounds is formed; they were separated by chromatography on silicic acid. One of the products was 3-methyl-5-piperidinoisoquinoline-7,8-quinone (VII). Its structure was confirmed by the results of elementary analysis and IR and mass spectrometry. A molecular ion peak with m/e 256 is observed in the mass spectrum of quinone VII; this is in agreement with the value calculated for $C_{15}H_{16}N_2O_2$. The subsequent fragmentation confirms the proposed structure. The mass spectrum of quinone VII contains intense peaks corresponding to fragments into which piperidinoquinones usually break down [8,9] under the influence of electron impact: m/e 228 (M − CO), 200 (M − 2CO), 175 (M − 2CO − C ≡ CH), 227 (M − 29), 213 (M − 43), and 84 [$(CH_2)_5N^+$].



VI VII VIII

The second quinone formed in the oxidation of phenol VI was identified as 3,5-dipiperidinoisoquinoline-7,8-quinone (VIII), which was previously obtained in [2]. We were unable to establish the structure of the third compound (IX), since it was found to be extremely labile and underwent changes on storage.

When the oxidation of VI was carried out with a smaller amount of piperidine (1.3 moles), ~50% of the starting compound remained in the reaction mixture, and a mixture consisting primarily of quinone VII was formed. An experiment with monitoring of the composition of the reaction mixture by TLC showed that quinone VII is gradually converted to a mixture of VIII and IX under the conditions of oxidative amination. Thus the oxidation of hydroxyisoquinoline VI is also accompanied by replacement of the methyl group at 3-C but takes place more slowly than in the case of corresponding isoquinolone II.



XI–XIII XIV XV, XVI

XI R = OCH_3; XII, XV R = $N(CH_2CH_2)_2O$; XIII R = $N(CH_2)_4$; XVI R = $N(CH_2)_5$

The next step in the research was the study of the possibility of amination of the heteroring in isoquinoline-5,8-quinones. For this we used 7-methoxyisoquinoline-5,8-quinone (XI), which was previously obtained from 7-methoxy-8-aminoisoquinoline (X) in three steps in an overall yield of 17% [10]. We found that the oxidation of amine X with potassium iminoxyldisulfonate makes it possible to obtain quinone XI in one step in 80% yield.

In contrast to isoquinoline-7,8-quinones, p-quinone XI reacts with morpholine or pyrrolidine to give only the usual products of substitution of the methoxy group (XII and XIII) without amination at 3-C. According to the TLC data, quinones XII and XIII are not aminated in the heteroring either when they are heated in alcohol with excess strong base of this type or a strong base such as pyrrolidine (pK_a 11.27) or under the conditions of oxidative amination. Not only the presence of a $C_8{=}O$ bond but also the participation of the carbonyl oxygen atom in the formation of a chelate complex, which increases the electrophilicity of 3-C, are evidently necessary for amination at 3-C. The chelate may be of either the V type or of the less stable XIV type, in which the complex is formed with the participation of both quinone carbonyl groups.

To confirm the reasons for the transmission of the effect of the carbonyl groups of quinones through the heteroring we carried out the oxidative amination of 6-hydroxyisoquinoline. Isoquinoline-5,6-quinones are not described in the literature. We supposed that they should be aminated in the heterocyclic ring, since the meso-

meric effect of the C_5=O bond is not transmitted to 3-C, and the C_6 = O bond is conjugated with the amine residue attached to 8-C. As we assumed, only 8-morpholino(piperidino)isoquinoline-5,6-quinones (XV and XVI) are formed as a result of the reaction of 6-hydroxyisoquinoline with morpholine (or piperidine).

EXPERIMENTAL

Monitoring of the course of the reactions and the purity of the products was accomplished by TLC on Silufol plates in a methanol–chloroform system (1:10). The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with Varian T-60 and Hitachi R-20 spectrometers with tetramethylsilane as the internal standard. The mass spectra were recorded with a Varian CH-6 spectrometer at an ionization chamber temperature of 180° and an ionizing voltage of 70 eV.

7-Hydroxy-1-quinolone (I). A mixture of 3.8 g (26 mmole) of 7-hydroxyisoquinoline [2] and 26 g of freshly fused and pulverized potassium hydroxide was heated in a stainless-steel crucible at 230° for 4 h with periodic stirring. It was then cooled and treated with 100 ml of water, and the resulting solution was neutralized with acetic acid. The precipitate was separated and dissolved in 50 ml of 3% NaOH solution, the solution was treated with charcoal, and the compound was reprecipitated with acetic acid. Recrystallization from aqueous methanol containing charcoal gave 1.05 g (25%) of colorless crystals with mp 315-316°. IR spectrum: 3170 br (associated OH) and 1662 cm^{-1} (CO). Found: C 67.1; H 4.6; N 8.5%. $C_9H_7NO_2$. Calculated: C 67.1; H 4.4; N 8.7%.

4-Methoxyhomophthalic Acid. A) A 14.5-g (0.33 mole) sample of a 55% emulsion of sodium hydride in mineral oil was added in portions with stirring at < 40° to 90 ml (0.7 mole) of acetoacetic ester, after which 29 g (0.125 mole) of 2-bromo-5-methoxybenzoic acid [11] mixed with 2.0 g (0.007 mole) of Cu_2Br_2 was added, and the mixture was stirred at 80° for 2 h. It was then cooled to room temperature and treated with 180 ml of water and 80 ml of ether. The ether layer was separated, and the aqueous layer was acidified with 20% H_2SO_4. The liberated oil was extracted with ether, the ether and excess acetoacetic ester were removed by vacuum distillation, and the residue (~ 38 g) was treated with a solution of 20 g of NaOH in 180 ml of water. A large portion of the residue dissolved when the mixture was heated, and the insoluble portion began to solidify on standing. After 1 h, the crystalline precipitate of side product III [5.0 g (15%)] was separated, and the filtrate was acidified with hydrochloric acid. The precipitated 4-methoxyhomophthalic acid was removed by filtration, washed with water, and dried to give 18.5 g (67%) of a product with mp 180-182° (mp 185-186° [12]).

The alkali-insoluble precipitate was ethyl 3-methyl-7-methoxyisocoumarin-4-carboxylate (III) with mp 83-84° (from alcohol). IR spectrum: 1710 (isocoumarin CO), 1723 (ester CO), 897, 881, 870, 840, and 785 cm^{-1}. PMR spectrum: 1.43 (CH_3, t, 3H), 2.40 (C-CH_3, s, 3H), 3.85 (OCH_3, s, 3H), 4.43 (OCH_2, q, 2H), 7.20 (6-H, q, 1H), 7.53 (5-H, d, J = 2.9 Hz, 1H), 7.65 (4-H, d, J = 8.7 Hz, 1H) ppm (see [13]). Found: C 64.1; H 5.4%. $C_{14}H_{14}O_5$. Calculated: C 64.1; H 5.4%.

B) A suspension of 0.5 g of ester III was refluxed for 1 h in 15 ml of 15% NaOH solution until a transparent solution formed, after which the solution was cooled and acidified with HCl, and the precipitate was removed by filtration, washed with water, and dried to give 0.35 g (87%) of a substance identical to the 4-methoxyhomophthalic acid obtained by method A.

3-Methyl-7-methoxy-1-isoquinolone. This compound was obtained by conversion of 4-methoxyhomophthalic acid to 4-acetyl-7-methoxyisochroman-1,3-dione by the method in [5]. The latter was converted, without purification, to 3-methyl-7-methoxy-1-isoquinolone by the method in [6] by the action of ammonium ammonium hydroxide. Workup gave a product with mp 213-215° (mp 214-215° [6]) in 56% yield.

3-Methyl-7-hydroxy-1-isoquinolone (II). A solution of 1.89 g (10 mmole) of 3-methyl-7-methoxyl-1-isoquinolone in 20 ml of 48% HBr was refluxed for 6 h, after which it was cooled and diluted with 40 ml of water. After 1 h, the precipitate was separated, washed with water, and dried to give 1.70 g (96%) of colorless plates with mp 320° (dec., from aqueous acetic acid). IR spectrum: 3250 br (associated OH) and 1660 cm^{-1} (CO). Found: C 68.1; H 5.3; N 8.3%. $C_{10}H_9NO_2$. Calculated: C 68.6; H 5.2; N 8.0%.

1-Hydroxy-3,5-dipiperidinoisoquinoline-7,8-quinone (IV). A) A 0.81-g (5 mmole) sample of I was added to a solution of 0.54 g (2.7 mmole) of copper acetate in a mixture of 4 ml (40 mmole) of piperidine and 5 ml of methanol, and the mixture was stirred in an oxygen atmosphere. After 5.5 h, 235 ml (10 mmole) of O_2 had been absorbed. The mixture was cooled to 0° and acidified with 3.5 ml of concentrated HCl in 5 ml of water, 40 ml of water was added, and the mixture was extracted with three 25-ml portions of chloroform. The chloroform solution was washed with water, dried with Na_2SO_4, and evaporated to a small volume. Quinone IV was isolated

chromatographically with a column (18 by 180 mm) filled with silicic acid. Workup gave 0.70 g (41%) of red acicular crystals with mp 220-221° (from ethyl acetate). IR spectrum: 1650, 1610 (CO), 1578, 1538 cm^{-1} (C = N, C = C). Found: C 67.0; H 7.1; N 12.3%. $C_{19}H_{23}N_3O_3$. Calculated: C 66.8; H 6.8; N 12.3%.

B) A 0.88-g (5 mmole) sample of hydroxy-1-isoquinolone II was oxidized and worked up as in the preparation of I. After 1.5 h, 320 ml (14 mmole) of O_2 had been absorbed. Workup gave 0.75 g (44%) of a substance that, according to its IR spectrum, the results of TLC, and its melting point, was identical to the product obtained by method A. PMR spectrum: 1.77 (β, γ-CH_2, unresolved multiplet, 12H), 3.20 (α-CH_2, unresolved multiplet, 4H), 3.80 (α'-CH_2, unresolved multiplet, 4H), 5.9 (6-H, s, 1H), 6.50 (4-H, s, 1H), and 13.7 ppm (OH, s, 1H). Found: C 67.1; H 6.6; N 12.3%. $C_{19}H_{23}N_3O_3$. Calculated: C 66.8; H 6.8; N 12.3%.

3-Methyl-7-hydroxyisoquinoline (VI). A solution of 3.0 g of 3-methyl-7-methoxyisoquinoline [6] in 20 ml of 48% HBr was refluxed for 6 h, after which it was cooled and neutralized with 10% ammonium hydroxide. The precipitate was removed by filtration, washed with water, and dried to give 2.5 g (90%) of colorless crystals with mp 252-255° (from aqueous alcohol). IR spectrum: 2500-3100 cm^{-1} br (OH). Found: C 74.7; H 5.7; N 8.6%. $C_{10}H_9NO$. Calculated: C 75.4; H 5.7; N 8.8%.

Oxidation of 3-Methyl-7-hydroxyisoquinoline (VI). A solution of 0.32 g (2 mmole) of VI and 0.1 g (0.5 mmole) of copper acetate in a mixture of 0.8 ml (8 mmole) of piperidine and 3 ml of methanol was stirred in an oxygen atmosphere for 1.5 h, during which 130 ml (5.8 mmole) of O_2 was absorbed. Chloroform (30 ml) was added to the reaction mixture, and the resulting solution was washed with water and dried with Na_2SO_4. According to the TLC data, the chloroform solution contained three substances: IX (R_f 0.58), VII (R_f 0.72), and VIII (R_f 0.82). The quinones were separated with a column filled with 30 g of silicic acid (elution with ethyl acetate). The order of emergence of the quinones from the column differed from the order observed in the case of TLC in a methanol–chloroform system. Workup up the first fraction yielded 150 mg of dark-red crystals of quinone IX with mp 140° (dec.). IR spectrum: 1714, 1697, 1629 (CO), 1578, and 1533 cm^{-1} (C = N, C = C). Workup of the second fraction gave 126 mg (19%) of quinone VIII. This product was identical to a genuine sample [2] of 3,5-dipiperidinoisoquinoline-7,8-quinone with respect to its melting point, IR spectrum, and R_f value. Workup of the third fraction yielded 120 mg (23%) of orange-red crystals of quinone VII with mp 128-130°. IR spectrum: 1694, 1633 (CO), 1591, 1577, and 1536 cm^{-1} (C = N, C = C). Found: C 70.2; H 6.2; N 10.9%. $C_{15}H_{16}N_2O_2$. Calculated: C 70.3; H 6.3; N 11.0%.

7-Methoxy-8-aminoisoquinoline (X). A 1-g sample of Raney nickel was added to a suspension of 11.0 g (0.054 mole) of 7-methoxy-8-nitroisoquinoline [14] in 80 ml of ethanol, after which 11 ml (0.19 mole) of 85% hydrazine hydrate was added dropwise with stirring at 60° in the course of 30 min. The mixture was then refluxed for 1 h, after which it was treated with charcoal and filtered hot. The filtrate was diluted with 550 ml of warm water, and the mixture was cooled. The precipitated crystals were separated, dried, and recrystallized from benzene to give 7.1 g (76%) of a product with mp 152-154° (mp 153-155° [10]).

7-Methoxyisoquinoline-5,8-quinone (XI). A solution of 1.50 g (8.6 mmole) of amine X in 70 ml of methanol was added at 20° with stirring in the course of 30 min to a solution of 5.0 g (18.7 mmole) of potassium iminoxyldisulfonate and 3.3 g (24 mmole) of $NaH_2PO_4 \cdot H_2O$ in 200 ml of water. A light-yellow precipitate began to form immediately. The reaction mixture was stirred for 4 h and was then allowed to stand overnight at 20°. The precipitated quinone XI was separated, washed with water, dried, and recrystallized from methanol to give 1.30 g (80%) of a product with mp 215-216° (dec.). (mp 215-216° [10]). IR spectrum: 1678, 1652 (CO), 1600, 1582, and 1562 cm^{-1} (C = N, C = C).

7-Morpholinoisoquinoline-5,8-quinone (XII). A 0.3-ml (3.3 mmole) sample of morpholine was added to a suspension of 0.19 g (1 mmole) of quinone XI in 16 ml of absolute alcohol, and the mixture was refluxed for 1.5 h. It wash then cooled, and the precipitate was separated, washed with alcohol, and dried to give 0.17 g (70%) of red crystals with mp 160-161° (mp 158-160° [10]). IR spectrum: 1674, 1640 (CO), 1585, and 1564 cm^{-1} (C = N, C = C).

7-Pyrrolidinoisoquinoline-5,8-quinone (XIII). A 0.42 ml (5 mmole) sample of pyrrolidine was added to a suspension of 0.19 g (1 mmole) of quinone XI in 5 ml of absolute alcohol, and the mixture was stirred for 30 min. The reaction mixture became red immediately, and a voluminous precipitate began to form. The reaction product was removed by filtration, washed with 1 ml of alcohol, and dried to give 0.21 g (92%) of red acicular crystals with mp 199-201° (dec.). IR spectrum: 1680, 1620 (CO), 1588, and 1565 cm^{-1} (C = N, C = C). Found: C 68.3; H 5.1; N 12.6%. $C_{13}H_{12}N_2O_2$. Calculated: C 68.4; H 5.3; N 12.3%.

6-Methoxyisoquinoline. A mixture of 3.5 g (21 mmole) of 6-methoxy-1,2,3,4-tetrahydroisoquinoline [15], 3.0 g of 10% Pd on carbon, and 15 ml of naphthalene was stirred and heated at 200-205° for 2 h, after which it

was cooled and the solid mass was dissolved in ether. The catalyst was removed by filtration, and the ether solution was extracted with three 10-ml portions of 3 N HCl solution. The aqueous solution was extracted with ether and made alkaline with 20% NaOH solution. The precipitated 6-methoxyisoquinoline was extracted with ether, the ether solution was dried with KOH, the ether was removed by distillation, and the residue was fractionated to give 2.0 g (59%) of a product with bp 132-135° (5 mm). The hydrochloride had mp 214-216° (mp 216° [16]).

6-Hydroxyisoquinoline. This compound was obtained in 66% yield by demethylation of 6-methoxyisoquinoline by refluxing with 48% HBr, as in the case of VI. The colorless crystals had mp 218-220° (dec.) [mp 220° (dec.) [17]].

8-Morpholinoisoquinoline-5,6-quinone (XV). A solution of 0.29 g (2 mmole) of 6-hydroxyisoquinoline and 0.01 g (0.05 mmole) of copper acetate in a mixture of 0.4 ml (4.4 mmole) of morpholine and 2.5 ml of methanol was stirred in an oxygen atmosphere until gas absorption ceased (2 h). Chloroform (30 ml) was added to the reaction mixture, and the resulting solution was washed with water and 2% acetic acid solution and dried with Na_2SO_4. The chloroform was removed by vacuum distillation, and the residue was crystallized by trituration with alcohol to give 0.21 g (43%) of red crystals with mp 160-162° (from alcohol). IR spectrum: 1707, 1645 (CO), 1593, 1577, and 1540 cm^{-1} (C = N, C = C). PMR spectrum: 3.25-3.68 (N–CH_2, unresolved multiplet, 4H), 3.68-4.08 (O–CH_2, unresolved multiplet, 4H), 6.03 (7-H, s, 1H), 7.68-8.08 (4H, unresolved multiplet, 1H), and 8.30-9.35 ppm (1-H, 3-H, unresolved multiplet, 2H). Found: C 63.8; H 5.1; N 11.3%. $C_{13}H_{12}N_2O_3$. Calculated: C 63.9; H 5.0; N 11.5%.

8-Piperidinoisoquinoline-5,6-quinone (XVI). The method used to prepare XV was employed to obtain this compound from 0.29 g (2 mmole) of 6-hydroxyisoquinoline in the presence of 8 mmole of piperidine. Quinone XVI was isolated by chromatography on silicic acid [elution with methanol-chloroform (1:20)]. Work-up gave 0.20 g (41%) of dark-red crystals with mp 137-138°. IR spectrum: 1705, 1629 (CO), 1588, 1574, and 1536 cm^{-1} (C = N, C = C). Found: C 68.9; G 5.9; N 11.7%. $C_{14}H_{14}N_2O_2$. Calculated: C 69.4; H 5.8; N 11.6%.

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