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Quinone Imines with a Fused Azine Ring: I. Synthesis and Hydrochlorination of 5-(*p*-Tolylsulfonylimino)quinolin-8-one

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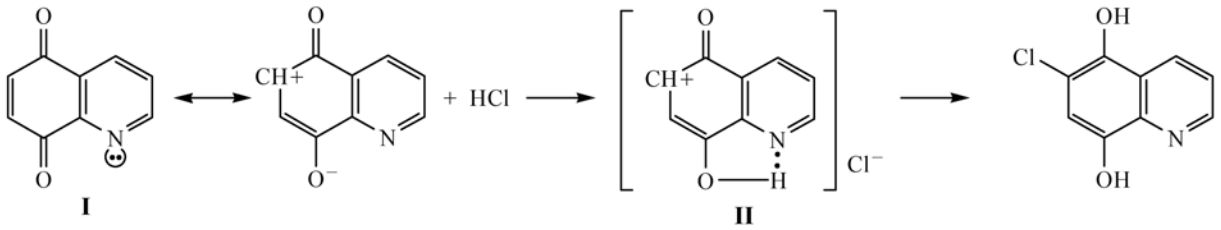
Abstract—5-(*p*-Tolylsulfonylimino)quinolin-8-one was synthesized, and its reaction with hydrogen chloride was studied. The reaction leads to formation of 7-chloro-8-hydroxy-5-(*p*-tolylsulfonylamino)quinoline hydrochloride.

Quinoline-5,8-diones attract attention due to their versatile biological activity. Their analogs with an endocyclic nitrogen atoms are structural fragments of most marine alkaloids [1]. Studies in the field of synthesis and transformations of quinoline-5,8-dione imines are very interesting from the viewpoint of controlling the reactivity of the quinoid ring through variation of substituent at the imino nitrogen atom, as well as of the position and electron-acceptor properties of the nitrogen atom in the fused pyridine ring. Up to now, only fragmentary data have been published on N-substituted 5-iminoquinolin-8-ones: 5-(hydroxyphenylimino)quinolin-8-ones [2, 3], *N*-aryl quinone imines of the indoaniline series [4–6], and *N*-hydroxy derivatives were reported [7]. *N*-Arylsulfonyl quinone imines of the quinoline series were not studied at all.

Quinoline-5,8-dione (**I**) is known to react with hydrogen chloride according to the 1,4-addition pattern (Scheme 1), resulting in formation of the corresponding 6-chloro derivative [8]. This reaction path is favored by the following factors: (1) the presence of an electron-acceptor endocyclic nitrogen atom increases the positive charge on the neighboring carbonyl carbon atom (C^8=O); (2) intermediate **II** formed by protonation of the carbonyl group is stabilized via intramolecular H-bonding.

We have synthesized 5-(*p*-tolylsulfonylimino)quinolin-8-one (**III**) as the first representative of *N*-arylsulfonyl quinone imines of the quinoline series and examined its reaction with hydrogen chloride with a view to elucidate the effect of arylsulfonylimino group in the 5-position on the reactivity of these compounds. By nitrosation of 8-hydroxyquinoline (**IV**) we obtained 8-hydroxy-5-nitrosoquinoline hydrochloride (**V**) (Scheme 2). Compound **V** was reduced to 5-amino-8-hydroxyquinoline dihydrochloride (**VI**) by reaction with tin(II) chloride dihydrate in concentrated hydrochloric acid. This procedure allowed us to avoid isolation of the ditin salt of amine **VI** and its subsequent decomposition with hydrogen sulfide. Treatment of dihydrochloride **VI** with *p*-toluenesulfonyl chloride in an alcohol–pyridine mixture afforded 8-hydroxy-5-(*p*-tolylsulfonylamino)quinoline which was converted into the corresponding hydrochloride **VII** for convenience in handling and storing. The most difficult stage in the synthesis of quinone imine **III** was oxidation of **VII**. The use of conventional reagents, such as lead tetraacetate in acetic acid, potassium hexacyanoferrate(III), or sodium hypochlorite in alkaline medium, was inefficient because of the low selectivity for formation of target quinone imine **III**. We succeeded in obtain-

Scheme 1.



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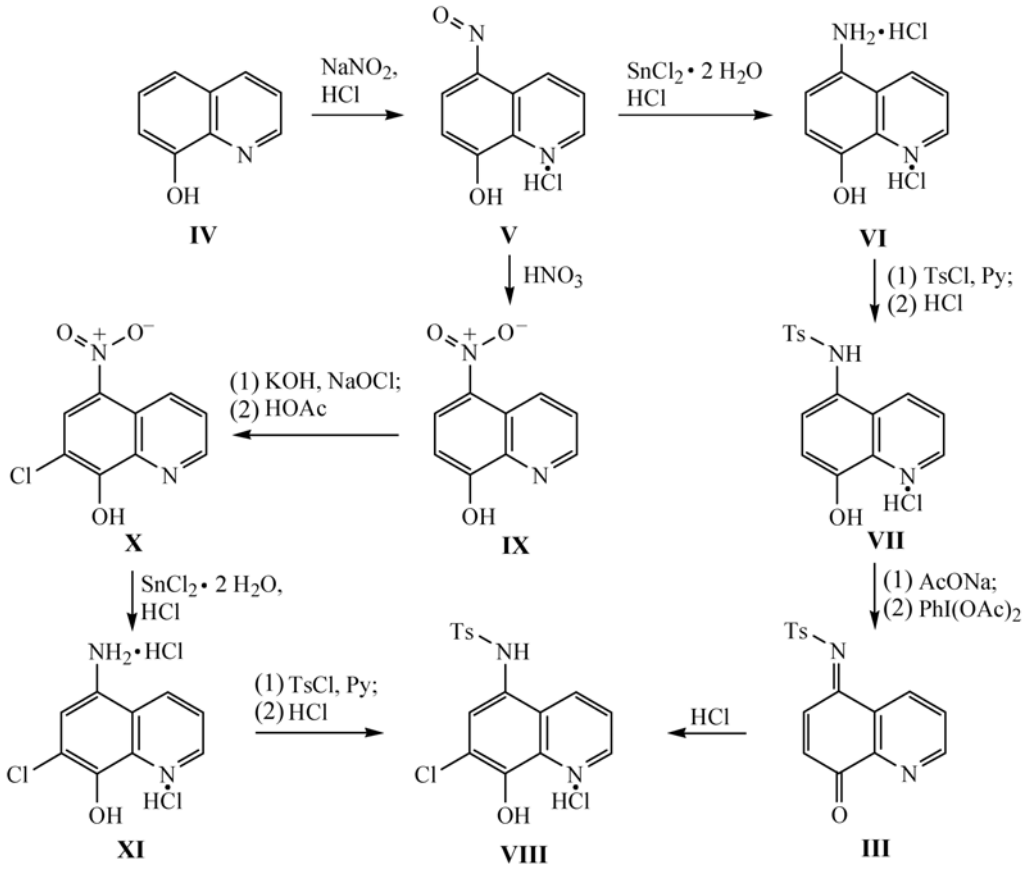
Scheme 2.



ing compound **III** in 90% yield by oxidation of **VII** with (diacetoxyiodo)benzene in glacial acetic acid after preliminary treatment of the substrate with sodium acetate.

The reaction of quinone imine **III** with hydrogen chloride was expected to give both 1,4-addition products (due to the presence of an arylsulfonylimino group [9]) and 6,3-adduct (due to the presence of electron-acceptor endocyclic nitrogen atom). The site of chlorine addition to the quinoid ring of **III** was proved by independent synthesis of 7-chloro-8-hydroxy-5-(*p*-tolylsulfonylamino)-quinoline which was isolated and identified as hydrochloride **VIII**. For this purpose, 8-hydroxyquinoline (**IV**) was converted into 8-hydroxy-5-nitroquinoline (**IX**). Compound **IX** was treated with sodium hypochlorite in alkaline medium to obtain 7-chloro-8-hydroxy-5-nitroquinoline (**X**) [8], and the latter was readily reduced with tin(II) chloride dihydrate in concentrated hydrochloric acid. The reduction product, 5-amino-7-chloro-8-hydroxyquinoline dihydrochloride (**XI**) was brought into reaction with *p*-toluenesulfonyl chloride in an alcohol–pyridine mixture, followed by treatment with hydrochloric acid. As a result, hydrochloride **VIII** was obtained. The same product was formed in the reaction of quinone imine **III** with hydrochloric acid. The structure of compounds **III**, **VII**, and **VIII** was confirmed by the data of IR and ^{1}H NMR spectroscopy.

Our results led us to conclude that replacement of the oxygen atom in the C^5=O carbonyl group of quinoline-5,8-dione by arylsulfonylimino group reduces the effect of the nitrogen atom in the pyridine ring on the reactivity of the quinoid system. Therefore, the reaction with hydrogen chloride follows the 1,4-addition pattern with formation of the corresponding 7-chloro derivative.

EXPERIMENTAL

The IR spectra of compounds **III**, **VII**, and **VIII** were recorded on a Specord 75IR spectrometer in KBr. The ^{1}H NMR spectra were obtained on a Varian VXR-300 instrument from solutions in DMSO-d_6 using TMS as internal reference. It should be noted that hydrochlorides **VII** and **VIII** with dimethyl sulfoxide give rise to exchange reaction leading to formation of dimethylsulfoxonium chloride and the corresponding free quino-

line bases; protons of the pyridine ring in the latter appear in the ^{1}H NMR spectrum as an *ABC* spin system. The purity of compounds **III** and **VI**–**XI** was checked by TLC on aluminum oxide (**III**, **VI**, **IX**–**XI**) or silica gel (**VII**, **VIII**) using BuOH–AcOH–H_2O, 4 : 5 : 1 (**IV**–**XI**), or EtOAc (**III**) as eluent. Spots were visualized by treatment with gaseous ammonia (**IX**, **X**), by UV light (**VII**, **VIII**), or by the indophenol reaction [10] with α-naphthol (**III**). Satisfactory elemental analyses for nitrogen and sulfur were obtained.

8-Hydroxy-5-nitrosoquinoline hydrochloride (V) was synthesized by nitrosation of 11.6 g of 8-hydroxyquinoline (**IV**) in hydrochloric acid according to the procedure described in [8]. Yield 15.7 g (95%). The product was brought into further synthesis without additional purification.

5-Amino-8-hydroxyquinoline dihydrochloride (VI). A suspension of freshly prepared hydrochloride **V** (obtained from 0.08 mol of compound **IV**), in 100 ml of concentrated hydrochloric acid was added with stirring at –1 to 10°C to a solution of 56.41 g (0.25 mol) of tin(II) chloride dihydrate in 25 ml of concentrated hydrochloric acid. The mixture was stirred for 1 h, and the precipitate was filtered off and recrystallized from dilute hydrochloric acid. Yield 13.7 g (73%, calculated on quinoline **IV**). Brown crystals, mp 245–246 °C (decomp.); published data [3]: mp 243°C.

8-Hydroxy-5-(*p*-tolylsulfonylamino)quinoline hydrochloride (VII). Pyridine, 6.5 ml, and *p*-toluenesulfonyl chloride, 4 g (0.021 mol), were added with stirring at room temperature to a solution of 4.6 g (0.02 mol) of amine **VI** in 25 ml of ethanol. The mixture was stirred for 2 h, left to stand for 24 h, and poured into 150 ml of an ice–water mixture. The precipitate was filtered off, washed with distilled water, and added to 50 ml of 15% hydrochloric acid, and the mixture was heated to the boiling point and cooled to 0°C. The precipitate of crude product **VII** was filtered off, washed with concentrated hydrochloric acid, and dried. Yield 50%. The product was recrystallized from 15–18% hydrochloric acid or glacial acetic acid. Yellow finely crystalline substance, mp 252–256°C (decomp.). IR spectrum, ν, cm^{-1}: 1358, 1160 (SO_2). ^{1}H NMR spectrum, δ, ppm: 2.352 s (3H, CH_3), 7.323 d (2H, H_{arom}, J = 8.4 Hz), 7.516 d (2H, H_{arom}, J = 8.4 Hz), 7.111 d (1H, 7-H, J = 8.1 Hz), 7.379 d (1H, 6-H, J = 8.1 Hz), 7.961 d.d (1H, 3-H, J_1 = 5.4, J_2 = 8.6 Hz), 8.960 d.d (1H, 4-H, J_1 = 3.8, J_2 = 8.6 Hz), 9.060 d.d (1H, 2-H, J_1 = 3.8, J_2 = 5.4 Hz), 10.360 s (1H, NH), 11.890 s (1H, OH). Found, %: N 7.91; S 9.10. $C_{16}H_{14}N_2O_3S \cdot HCl$. Calculated, %: N 7.98; S 9.14.

5-(*p*-Tolylsulfonylimino)quinolin-8-one (III). (Diacetoxyiodo)benzene, 1.84 g (5.7 mmol), was added with stirring to a suspension of 2 g (5.7 mmol) of hydrochloride **VII** and 0.47 g (5.7 mmol) of anhydrous sodium acetate in 8 ml of acetic acid. After 1 h, the precipitate was filtered off, washed with hexane, and dried. Yield 1.6 g (90%). The crude product was dissolved in dry chloroform, charcoal was added, the solution was filtered, and the filtrate was partially distilled off under reduced pressure without heating. The yellow finely crystalline precipitate was filtered off, dried, and stored at –10 to –5°C. The purified product begins to decompose at 177–178°C. IR spectrum, ν, cm^{-1}: 1312, 1147 (SO_2); 1692 (C=O); 1676 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.450 s (3H, CH_3), 7.525 d (2H, H_{arom}, J = 9 Hz), 7.975 d (2H, H_{arom}, J = 9 Hz), 7.170 d (1H, 7-H, J = 11.5 Hz), 8.295 d (1H, 6-H, J = 11.5 Hz), 7.790 d.d (1H, 3-H, J_1 = 4.5, J_2 = 9.0 Hz), 8.415 d.d (1H, 4-H, J_1 = 3.0, J_2 = 9.0 Hz), 9.015 d.d (1H, 2-H, J_1 = 3.0, J_2 = 4.5 Hz). Found, %: N 8.92; S 10.19. $C_{16}H_{12}N_2O_3S$. Calculated, %: N 8.97; S 10.26.

8-Hydroxy-5-nitroquinoline (IX) was synthesized by nitrosation of 8-hydroxyquinoline (**IV**), followed by oxidation of nitroso derivative **V** with nitric acid according to the procedure described in [11]. From 23.2 g of compound **IV** we obtained 18.6 g (61%) of the product as a greenish–yellow powder with mp 179–181°C (decomp.); published data [8, 11, 12]: mp 177–181°C.

7-Chloro-8-hydroxy-5-nitroquinoline (X) was synthesized by treatment of nitroso compound **IX** with sodium hypochlorite in alkaline medium according to the procedure reported in [8]. From 10 g of compound **IX** we obtained 8.5 g (71%) of product **X** as a bright orange powder with mp 238–240°C (decomp.), 239–240.5°C [8].

5-Amino-7-chloro-8-hydroxyquinoline dihydrochloride (XI). A solution of 34.2 g (0.15 mol) of tin(II) chloride dihydrate in 40 ml of concentrated hydrochloric acid was heated to 70°C, and 8.5 g (0.38 mol) of quinoline **X** was added with stirring. The mixture was stirred for 2.5 h at 90°C and cooled, the precipitate of dihydrochloride **XI** ditin salt was filtered off and dissolved in 450 ml of hot water, a stream of hydrogen sulfide was passed through the solution, the precipitate of tin(II) sulfide was filtered off, the filtrate was evaporated to a volume of 45–50 ml and cooled, and the precipitate of amine dihydrochloride **XI** was filtered off and dried. Yield 6.7 g (66%). The product was purified by recrystallization from dilute hydrochloric acid. Decomposition point 267.5–269.5°C. Found, %: N 10.41. $C_9H_7ClN_2O \cdot 2HCl$. Calculated, %: N 10.47.

7-Chloro-8-hydroxy-5-(*p*-tolylsulfonylamino)-quinoline hydrochloride (VIII). (a) *p*-Toluenesulfonyl chloride, 2.8 g (0.015 mol), was added to a solution of 4 g (0.015 mol) of compound **XI** in a mixture of 7 ml of pyridine and 30 ml of ethanol. The mixture was stirred for 2 h at room temperature, left to stand for 24 h, and poured onto 200 g of crushed ice. The precipitate was filtered off, washed with water, and transferred (while wet) into 45–50 ml of 10% hydrochloric acid. The mixture was stirred for 30 min, and the precipitate of compound **VIII** was filtered off and dried. Yield 4.6 g (80%, calculated on **XI**). The product was purified by recrystallization from dilute hydrochloric acid. Yellowish–light green crystals, mp 224–225°C.

(b) Quinone imine **III,** freshly prepared from 1.5 g (4.3 mmol) of hydrochloride **VII**, was dispersed in 9 ml of acetic acid, 4 ml of concentrated hydrochloric acid was added with stirring, and the mixture was stirred for 10 min and poured into 30 ml of water containing ice. The precipitate was filtered off, washed on a filter with water, and dried. Yield of the crude product 0.75 g (46%, calculated on **VII**). The crude product was purified by double recrystallization from glacial acetic acid. Greenish–grey needles, mp 224.5–225°C. The product showed no depression of the melting point on mixing with a sample prepared from amine **XI** as described in *a*. IR spectrum, ν, cm^{-1}: 1317, 1155 (SO_2), 3241 (NH), 3295 (OH). ^1H NMR spectrum, δ, ppm: 2.343 s (3H, CH_3), 7.095 s (1H, 6-H), 7.321 d (2H, H_{arom}, J = 8.2 Hz), 7.540 d (2H, H_{arom}, J = 8.2 Hz), 7.677 d.d (1H, 3-H, J_1 = 4.5, J_2 = 7.7 Hz), 8.532 d.d (1H, 4-H, J_1 = 3.3, J_2 = 7.7 Hz), 8.958 d.d (1H, 2-H, J_1 = 3.3, J_2 = 4.5 Hz), 10.402 s (1H, NH), 11.989 s (1H, OH). Found, %: N 7.20; S 8.28. $C_{16}H_{13}ClN_2O_3S \cdot HCl$. Calculated, %: N 7.27; S 8.32.

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