Approach to the synthesis of 8-nitroquinoline-2-carboxylic acid in high yield

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A synthesis of 8-nitroquinoline-2-carboxylic acid was optimized, using the following basic scheme of transformations: 1) nitration of 2-methylquinoline with subsequent separation of a mixture of isomeric 8-nitro- and 5-nitro-2-methylquinolines; 2) oxidation of the methyl group in 2-methyl-8-nitroquinoline (including consecutive steps of bromination and hydrolysis in aqueous sulfuric acid). A new method for the separation of isomeric 8-nitro- and 5-nitro-2-methylquinolines was suggested. The optimal conditions for the final step of hydrolysis were selected, which gave almost quantitative yield of 8-nitroquinoline-2-carboxylic acid.

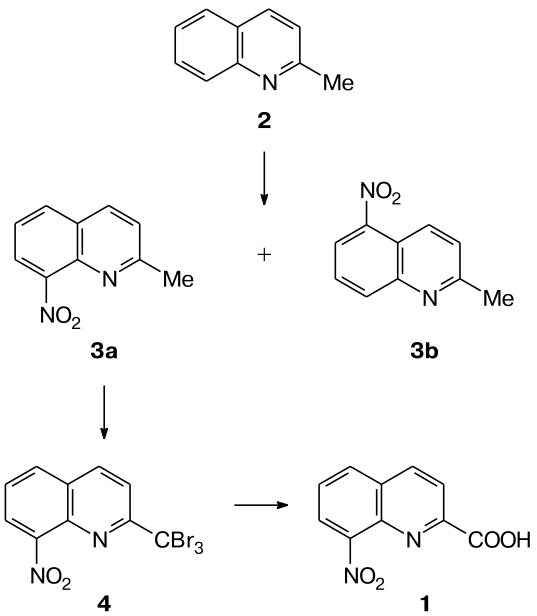
Key words: 8-nitroquinoline-2-carboxylic acid, synthesis, separation of isomers, acid hydrolysis.

8-Nitroquinoline-2-carboxylic acid (**1**) is a useful reactant in the synthesis of a number of compounds important for the development of high-technology productions, pharmacy, and medicinal studies. For example, in the patent[1] it is indicated that acid **1** can be used in the synthesis of efficient therapeutical agents, pharmaceutical compositions, and antibiotics. A fluorescent chemosensor for determination of anions in living organisms was develop based on 8-nitroquinoline-2-carboxylic acid 4-isobutoxy derivative.[2] Apart from that, the acid **1** itself and some compounds derived from it showed high activity against the causative agent of anthroponotic visceral leishmaniasis.[3,4]

There are known several approaches to the synthesis of compound **1**. Nitration of quinoline-2-carboxylic acid gives 8- and 5-nitro isomers of compound **1** (see Ref. 1). The difficulties in the separation of the isomers and the expensive starting reagent are the main disadvantages of this approach. The low yield (13%) and high cost characterize another method for the preparation of **1** through the oxidation of 10-nitrobenzo[*c*]quinolisinium perchlorate with potassium permanganate.[5] Apart from that, compound **1** can be obtained by the reaction of *o*-nitroaniline with some reagents (crotonic aldehyde in the presence of arsenic pentoxide[6] or phosphotungstic acid,[7] vinyl *n*-butyl ether in the presence of nitrobenzene,[8] paraldehyde[9]) with subsequent oxidation of the methyl group in 2-methyl-8-nitroquinoline obtained. However, these synthetic procedures also give low yields of **1** (15—45%), use expensive and toxic starting reagents, laborious isolation of the target product.

The most convenient pathway for the preparation of **1** includes nitration of readily available 2-methylquinoline (**2**) with subsequent oxidation of the methyl group in the intermediate 2-methyl-8-nitroquinoline (**3a**) (Scheme 1).

Scheme 1



Procedures for the carrying out the first step (nitration of compound **2**) are considered in the works.[3,10—13] They differ in the composition of the nitrating mixture (concentrated sulfuric and nitric acids; sulfuric acid and potassium or ammonium nitrate, *etc.*) and in the method of separation of isomers **3a** and **3b** (fractional

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crystallization from methanol or propanol, chromatographic separation).

The yields of the isomers vary: 35—45% for **3a** and 40—50% for **3b** (see Refs 3 and 10—13).

The final step in the preparation of **1** is the oxidation reaction of the methyl group in **3a** through the intermediate bromination with the formation of compound **4** and subsequent hydrolysis to the target product (see Scheme 1).[8,10] The bromination step poses no problems, compound **4** is formed in quantitative yield. However, the final step of hydrolysis of **4** in 20% aqueous sulfuric acid leads to the target product **1** in low (~16%) yield.[8,10] The yield of the target product **1** was increased to 50% by increasing the reaction time and concentration of sulfuric acid (to 27.5%).[14] It is probable that varying such parameters as the concentration of sulfuric acid and hydrolysis time, the yield of **1** can be increase to the values close to 100%. However, such studies have not been carried out earlier. In this connection, the present work is directed on the search of the optimal conditions for the final step of hydrolysis of **4** (see Scheme 1) in order to increase the yield of **1**. An additional problem to be solved consisted in the search for an alternative, more convenient method (as compared to fractional crystallization and chromatography) for the separation of isomers **3a** and **3b**, which would considerably simplify the synthesis of 8-nitroquinoline-2-carboxylic acid (**1**).

Results and Discussion

Separation of 8- and 5-nitro isomers 3a and 3b. One of the methods for the separation of 8- and 5-nitro isomers **3a** and **3b** is based on the different basicity of these compounds.[15,16] In fact, it was shown[17] that the nitro group at position 5 can decrease the basicity of the quinoline molecule as compared to its 8-nitro isomer by more than two orders of magnitude (the equilibrium constant of the reaction of the corresponding quinolinium ion with hydroxide ion with the formation of a "pseudobase" is given in the work,[17] the equilibrium constant of the reversed reaction can be considered as the basicity of the "pseudobase" formed). However, despite the large difference in the basic properties of compounds **3a** and **3b**, such a method for their separation is not widely used, since the optimal pH values for the precipitation of each of the isomers were not found. In the present work, a controlled increase in the pH of the solution (from 1 to 10) of a mixture of hydrochlorides of isomers **3a** and **3b** was used to find out that 8-nitro isomer **3a** precipitates as an individual compound within pH 2—4, whereas 5-nitro isomer **3b** precipitates at pH 6—10.

Hydrolysis 2-tribromomethyl-8-nitroquinoline (4). Table 1 summarizes the results of hydrolysis of **4** in solutions of sulfuric acid with different concentrations. In the first entry (Table 1), we reproduced a procedure described earlier[14] with an increased time of hydrolysis. After 26 h, the reaction mixture completely homogenized (compound **4** dissolved). Thus, the yield of **1** was increase almost twofold as compared to the results reported in the work.[14] Most likely, the reason for the moderate yield of **1** given in the patent publication[14] consists in the fact that the authors stopped hydrolysis before it reached completion, indicating that the reaction mixture contained unreacted precipitate.

Table 1. Dependence of the yield of **1** on the mass fraction of H_2SO_4 in the hydrolysis reaction of **4**

Entry	ω (H_2SO_4) (%)	τ/h	Yield of **1** (%)
1	27.5	26	96
2	30	24	97.2
3	35	20	78.6

Note: τ is the hydrolysis time.

In other entries, we varied the concentration of sulfuric acid. It is seen from the data in Table 1 that an increase in the concentration of H_2SO_4 decreases the hydrolysis time (a criterion of the hydrolysis completion was the time required for the dissolution of **4** in the reaction mixture). However, the entry with 35% aqueous H_2SO_4 led to the formation of side products (a black precipitate) and a considerable decrease in the yield of **1**. The use of 30% aqueous solution of H_2SO_4 for hydrolysis **4** turned out to be the optimal.

In conclusion, we have developed a number of approaches allowing one to considerably lower the cost and simplify the process of preparation of 8-nitroquinoline-2-carboxylic acid. First, we suggested a simple (as compared to the known) method for the isolation of the intermediate 2-methyl-8-nitroquinoline (**3a**). Second, we optimized the final step of hydrolysis of 2-tribromomethyl-8-nitroquinoline (**4**), that increased the yield of the target 8-nitroquinoline-2-carboxylic acid **1** from ~50% to almost quantitative. We have developed a criterion of the hydrolysis completion of **4**: an entire dissolution of 2-tribromomethyl-8-nitroquinoline (**4**). We found an optimal concentration of sulfuric acid (30%) for the most rapid proceeding of the hydrolysis process and the formation of the minimum amount of side products.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX 500 spectrometer (500.13 MHz) at a temperature of 298 K, using tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan MAT, INCOS 50 instrument with injection of compounds in the localization area at the energy of ionizing electrons of 70 eV. Melting points were measured on a Boetius PH MK 05 heating stage with an observation device and were corrected. Elemental analysis was carried out on a Vario Micro cube CHNS/O elemental analyzer.

Synthesis of 2-methyl-8-nitroquinoline was based on the procedure described in the literature.[16] Ammonium nitrate (48 g, 0.6 mol) was added in portions to a solution of 2-methylquinoline bisulfate (120.6 g, 0.5 mol) in concentrated sulfuric acid (200 mL) with stirring at 10—15 °C over 20 min. The mixture was stirred for 1 h, then poured onto ice (800 g). The resulting mixture was alkalized with 25% aqueous solution of ammonia to pH 10—11, maintaining the temperature below 20 °C. A precipitate formed was stirred for another 2 h, filtered, washed with water (3×100 mL) on the filter. The mixture of 8-nitro- and 5-nitro-2-methylquinolines was suspended into water (700 mL), followed by a gradual addition of concentrated hydrochloric acid until a complete dissolution of the suspension (pH of the solution <1). The resulting solution was filtered from a small amount of the resin-like impurities, the filtrate was gradually diluted with a 30% solution of NaOH with stirring and a temperature below 25 °C). A precipitate formed was collected within pH 2—4. This precipitate was practically pure 2-methyl-8-nitroquinoline. For final purification, it was recrystallized from isopropyl alcohol to obtain 2-methyl-8-nitroquinoline (35.2 g, 37.4% on theoretical), m.p. 138.5—139 °C. Found (%): C, 63.99; H, 4.45; N, 14.74. $C_{10}H_8N_2O_2$. Calculated (%): C, 63.82; H, 4.28; N, 14.89; O, 17.00. ^{1}H NMR, δ: 2.77 (s, 3 H, Me); 7.41 (d, 1 H, C(3)H, J = 9.0 Hz); 7.53 (dd, 1 H, C(6)H, J = 9.0 Hz, J = 8.5 Hz); 7.94—7.97 (m, 2 H, C(5)H + C(4)H); 8.11 (d, 1 H, C(7)H, J = 9.0 Hz). MS, m/z (I/I_{max} (%)): 188 [M] (100), 158 (30), 142 (20), 130 (75), 115 (85), 103 (20), 89 (28).

A precipitate collected at pH 6—10 was practically pure 2-methyl-5-nitroquinoline. Its further purification from the traces of 8-nitro isomer consisted in the extraction with hot hexane (8-nitro isomer is poorly soluble in hexane and remained in the precipitate) to obtain 5-nitro isomer (40.0 g, 42.5% on theoretical). The fraction collected at pH 4—6 was a mixture of both isomers.

Synthesis of 8-nitro-2-tribromomethylquinoline.[9] 2-Methyl-8-nitroquinoline (**3a**) (28.2 g, 0.15 mol) was suspended in glacial acetic acid (600 mL) saturated with anhydrous sodium acetate (~20 °C), followed by a dropwise addition of a solution of bromine (80 g, 0.5 mol) in glacial acetic acid (200 mL) with stirring over 5 h. The reaction temperature was maintained within 20—25 °C. Then, the mixture was heated to 85 °C and allowed to stand at this temperature for 30 min and poured into water (2.5 L). A precipitate formed was filtered and washed with cold (10—12 °C) water (2×60 mL) on the filter to obtain practically pure product. The yield was 62.85 g (98.6% on theoretical), m.p. 118—118.5 °C. Found (%): C, 28.43; H, 1.40; N, 6.8. $C_{10}H_5Br_3N_2O_2$. Calculated (%): C, 28.27; H, 1.19; Br, 56.42; N, 6.59; O, 7.53. ^{1}H NMR, δ: 7.65—7.75 (m, 1 H, C(6)H); 8.09 (d, 1 H, C(5)H, J = 9.0 Hz); 8.13 (d, 1 H, C(4)H, J = 8.0 Hz); 8.36—8.38 (m, 2 H, C(3)H + C(7)H). MS, m/z (I/I_{max} (%)): 345 (100), 299 (20), 286 (20), 265 (15).

Synthesis of 8-nitroquinoline-2-carboxylic acid. The synthesis was carried out with sulfuric acid of different concentrations indicated in Table 1. 2-Tribromomethyl-8-nitroquinoline (25.5 g, 60 mmol) was suspended in aqueous sulfuric acid (485 mL). The reaction mixture was refluxed with stirring until complete dissolution of **4**, cooled to 80 °C, and poured into water (500 mL). The reaction mixture was hot filtered from the side products and poured into water (800 mL). After 10—12 h (at ~20 °C), a precipitate formed was filtered, washed with cold water (20 mL) on the filter. An analytical sample was obtained by recrystallization from isopropyl alcohol. The yields of compound **1** are given in Table 1. Melting point of compound **1** was 176—177 °C. Found (%): C, 55.02; H, 3.03; N, 12.71. $C_{10}H_6N_2O_4$. Calculated (%): C, 55.05; H, 2.77; N, 12.84; O, 29.33. ^{1}H NMR, δ: 7.90 (dd, 1 H, C(6)H, J = 8.5 Hz, J = 9.0 Hz); 8.27 (d, 1 H, C(3)H, J = 9.0 Hz); 8.37 (d, 1 H, C(5)H, J = 8.5 Hz); 8.40 (d, 1 H, C(4)H, J = 9.0 Hz); 8.77 (d, 1 H, C(7)H, J = 9.0 Hz); 13.75 (br.s, 1 H, —COOH). MS, m/z (I/I_{max} (%)): 218 [M] (20), 174 (100), 157 (18), 127 (40), 116 (45), 101 (30).

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