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TECHNOLOGY OF PREPARING 8-HYDROXY-5-NITROQUINOLINE

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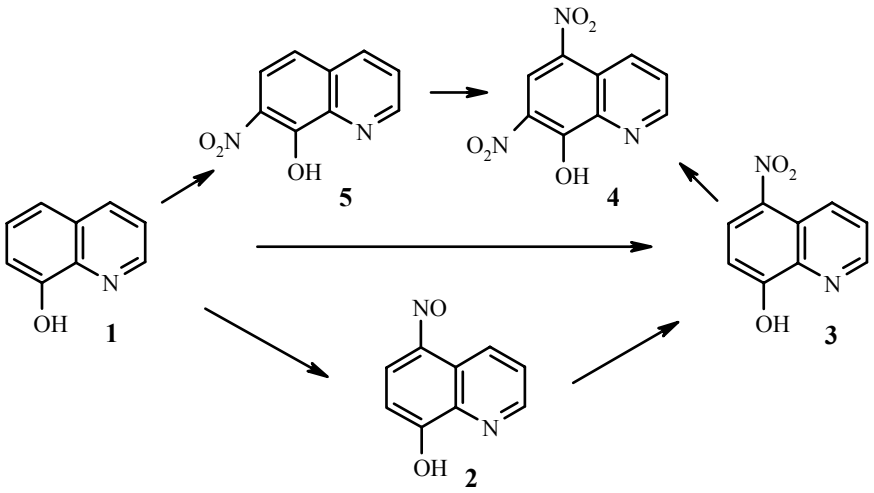
An efficient, two stage method is proposed for the preparation of 8-hydroxy-5-nitroquinoline based on the nitrosation of 8-hydroxyquinoline and subsequent oxidation of the nitroso derivative using nitric acid. The conditions for the nitrosation and oxidation of the 8-hydroxyquinoline (concentration of nitric acid, temperature, and reaction time) were optimized. A method for purifying the target compound is presented.

Keywords: 8-hydroxy-5,7-dinitroquinoline, 8-hydroxy-5-nitrosoquinoline, 8-hydroxy-5-nitroquinoline, 8-hydroxy-7-nitroquinoline, 8-hydroxyquinoline, nitration, nitrosation, oxidation, purification.

8-Hydroxy-5-nitroquinoline (with the synonyms 5-NOK, Nibiol, Nikinol, Nikopet, Nitroxoline, Niuron, Noxibiol, Noxin, Uritrol etc.) shows antibacterial activity towards Gram-positive and Gram-negative bacteria and is also effective in relation to certain fungi (e.g. the *Candida* strain). In contrast to other 8-hydroxyquinoline derivates 5-NOK is rapidly absorbed from the gastro-intestinal tract and is excreted unchanged by the kidneys as evidenced by the high concentration of the preparation in the urine. It is used for urinary tract infections (pyelonephritis, cystitis, urethritis, prostatitis etc.), for the prophylaxis of infections after operations on the kidneys and urinary tract, and with other illnesses involving microorganisms sensitive to the preparation. It is also effective towards microflora resistant to other antibacterial agents [1, 2].



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Several methods for preparing 8-hydroxy-5-nitroquinoline (**3**) have been reported in the literature. A direct Skraup type synthesis from 2-amino-4-nitrophenol [3] and also from 2,4-dinitrophenol [4] gives low yields of compound **3**.

Compound **3** can be prepared by direct nitration of 8-hydroxyquinoline (**1**) or by the oxidation of 8-hydroxy-5-nitrosoquinoline (**2**) [5]. The direct nitration of the hydroxyquinoline **1** using nitrating mixture in an acid medium (HNO_3-H_2SO_4) proceeds non selectively and gives a 75% yield of a mixture of the target compound **3**, its isomer **5**, and the dinitro derivative **4** [6]. The nitration of compound **1** by nitric acid in aqueous medium or in acetic acid [7] gives compound **3** in 45% yield. Nitration in alcoholic medium leads to an increase in the yield of **3** to 63% [8] but this is accompanied by the formation of a large amount of the side products 8-hydroxy-5,7-dinitroquinoline (**4**) and 8-hydroxy-7-nitroquinoline (**5**). Increasing the concentration of the nitric acid [9-11] or the temperature [12-14] leads to the formation of the intermediate compound **4**. In the presence of nitric acid this can further undergo degradation with opening of the benzene ring to form pyridine carboxylic acids [10, 15]. Several variants of a two stage synthesis of compound **3** *via* nitrosation of 8-hydroxyquinoline **1** and subsequent oxidation of the nitroso derivative **2** by different oxidants have been reported [8, 16-18].

In order to develop a method of preparing compound **3** suitable for industrial use we have chosen a two stage method of nitrosation of compound **1** using sodium nitrite in aqueous medium and subsequent oxidation of the nitroso compound **2** with nitric acid in acetic acid.

In the process of this work we have investigated the conditions for the nitrosation and the oxidation and found the most efficient variant for the preparation. Nitrosation of compound **1** was carried out by us using a modified Urbanski method [14] with sodium nitrite in dilute sulphuric acid. The effects of prolonged reaction time and temperature were studied in order to find the optimal. The maximum yield (up to 95%) with a high percentage nitroso derivative (**2**) content (98-99% by iodometric titration) was obtained at 15-20°C and a reaction time of 3 h. With oxidation of dry compound **2** according to method [19] the overall yield of compound **3** reached 60-70%.

The comparatively low yield of the final product can be rationalized in terms of the occurrence of competing reactions, amongst which the formation of the dinitro derivative **4** predominates. In addition, the technical material contains a significant amount of an admixture of the starting compound **2** which cannot be adequately separated by recrystallization from ethyl or isopropyl alcohol.

The addition of sodium nitrite (~1% of the mass of compound **2**) speeded up the start of the reaction and stabilized the yield of the target compound **3**. For the purpose of simplifying the technical process (excluding the drying and grinding of compound **2**) the oxidation reaction was carried out using an aqueous paste of the nitroso compound with addition of conc. HNO_3 to a suspension of the nitroso compound **2** in acetic acid and with stirring.

During the development of the optimal conditions for the oxidation we have studied the effect of the concentration of nitric acid (28-46%) and of the temperature (25-55°C) on the course of the reaction. The composition of the obtained compounds (content of **2** and **3**) was determined by UV spectroscopy. The maximum yields (up to 77%) of compound **3** were achieved at a nitric acid concentration of 32-34%, temperature of 35-40°C, and reaction time of 1.5 h.

Compound **3** forms a salt with both nitric acid and with base hence, for complete separation of the free base, it is necessary to create an acetate buffer solution and this is achieved by neutralization with a small excess of base and subsequent addition of acetic acid. Under these conditions compound **3** has its minimum solubility. The yield of technical product was 70-75%.

When checking the recommended method for purifying compound **3** [19, 20] it was found that a two fold recrystallization from ethyl alcohol and recrystallization from hydrochloric acid [21] did not permit a preparation with the required purity. Negative results were obtained using isopropyl or isobutyl alcohols and also ethyl acetate, dichloroethane, and toluene. Only recrystallization from acetone gave a material of satisfactory purity in a yield up to 70% [22]. We have proposed a method for the purification which consists of

recrystallization from acetone, removal by filtration of the insoluble side product **4**, and subsequent precipitation from the filtrate of compound **3** by distilled water. Using this method of purification the yield of pharmacopoeial material was 90-95% in terms of the technical product.

EXPERIMENTAL

8-Hydroxy-5-nitrosoquinoline (2). A. Compound **1** (73.43 g, 0.5 mol) was added to a solution of conc. H_2SO_4 (30 ml) in distilled water (667 ml) with vigorous stirring at 15-18°C. A solution of sodium nitrite (36.7 g) in water (67.8 ml) (34.7%) was added dropwise over 30-40 min at a reaction temperature of 18-20°C. The mixture obtained was held at this temperature for 3 h. The completeness of the nitrosation was checked by the presence of excess sodium nitrite in the reaction mixture (reaction with the Griess-Ilosvay reagent) and by the acidity of the medium (pH 1.0-2.0). The reaction product was cooled and basified at a temperature not exceeding 25°C using a 24% solution of sodium hydroxide to pH 10-11 and then acidified to pH 5.0-6.0 with glacial acetic acid. The precipitate was filtered off, washed with distilled water (3 × 250 ml), and dried for 1.5-2.0 h at 60-70°C to give compound **2** (84.6 g, 96%) of 98.57% purity (iodometric titration) with a decomposition temperature equal or greater than 235°C (according to [14] 235°C)

B. Under method A conditions to give compound **2** which, as a paste, was used at the oxidation stage without washing with distilled water.

8-Hydroxy-5-nitroquinoline (3). HNO_3 (d^{20} = 1.345) (0.32 ml) was added dropwise with stirring over 20 min to a homogenous suspension of compound **2** (25 g, 0.144 mol) in acetic acid (62.5 ml) at 20-30°C and held for 2 h at 25-30°C. After cooling to 0°C a solution of NaOH (24%, 260 ml) was added slowly to pH 10-11 with the temperature held at 20-25°C. The mixture was then cooled to 10-15°C over 30 min, filtered, and acetic acid (34 ml) was added to pH 5-6 and again cooled for 30 min to 10-15°C. The precipitate was filtered off, washed with distilled water (4 × 250 ml) to complete removal from the reaction of nitrate, sulphate, and acetate ions, and then washed with acetone (100 ml) and dried at 70-80°C to give compound **3** (26.6 g, 98%); mp 175-177°C.

A mixture of the technical material **3** (26.6 g), acetone (340 ml),and activated carbon (0.9 g) was refluxed for 1.25 h. The solution was filtered, distilled water (340 ml) was added, and the product was cooled. Filtration of the precipitate gave compound **3** (23.44 g, 87% based on the 8-hydroxyquinoline) with a material base content of 99-99.5% and mp 178-179.5°C.

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