NITRO DERIVATIVES OF 3-HYDROXYQUINOLINE

K. M. Dyumaev, E. P. Popova,
I. F. Mikhailova, L. I. Shibaeva,
and L. D. Smirnov

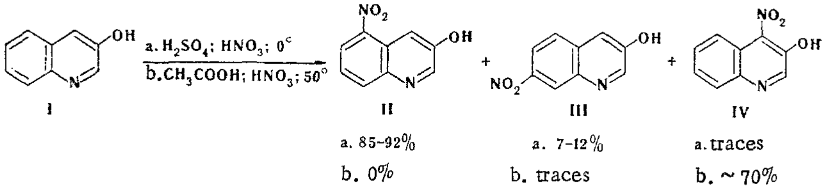
UDC 547.831.7:542.958.1

The nitration of 3-hydroxyquinoline with concentrated nitric acid in sulfuric acid at −30 to +30°C gives 5-nitro-3-hydroxyquinoline (85-92%) and 7-nitro-3-hydroxyquinoline (7-12%). 4-Nitro-3-hydroxyquinoline is formed in 70% yield by nitration in acetic acid. 4,5-Dinitro-3-hydroxyquinoline is formed by further nitration of 4- and 5-nitro-3-hydroxyquinolines.

It is known that a mixture of 5- and 8-nitroquinolines is formed by nitration of quinoline in sulfuric acid [1]. The introduction of a hydroxyl group into the pyridine ring in the 2 or 4 position leads to nitration in the 6 and 8 positions under the same conditions, while the formation of 3-nitro-2-(or 4)hydroxyquinoline is observed in nitration with concentrated nitric acid [2].

The nitration of 3-hydroxyquinoline (I) has not been studied. Only 6- and 8-nitro-3-hydroxyquinolines, which were obtained as side products in low yields by oxidation of the corresponding nitroquinolines with hydrogen peroxide, have been described in the literature [3-5].

We have studied the nitration of I under various conditions. When the nitration was carried out with an equimolecular amount of concentrated nitric acid in sulfuric acid at 0°C, 5-nitro-3-hydroxyquinoline (II) (85-92%), 7-nitro-3-hydroxyquinoline (III) (7-12%), and traces of 4-nitro-3-hydroxyquinoline (IV) are formed.



Changing the nitration temperature from −30 to +30° does not substantially change the ratio of the nitro isomers and does not lead to the formation of new compounds.

The structures of nitro derivatives II and III were proved by oxidative cleavage and were confirmed by the PMR spectra. m-Nitroaniline, the product of the decomposition of the resulting 6-nitroanthranilic acid [6], was isolated in the oxidation of nitro derivative II with potassium permanganate in alkaline media. The oxidation of isomers III under similar conditions gave 4-nitroanthranilic acid.

In the nitration of I with concentrated nitric acid in acetic acid we isolated only 4-nitro derivative IV. The best results (70% yield) were obtained by heating nitrate I in acetic acid at 50-60°. The structure of IV was proved by reduction to amino derivative V and subsequent diazotization and replacement of the diazo group by chlorine to give the known 4-chloro-3-hydroxyquinoline (VI).

4,5-Dinitro-3-hydroxyquinoline (VII) is formed by further nitration of isomer II in acetic acid or by nitration of IV in sulfuric acid. The results demonstrate that the position of the entering nitro group is determined mainly by the orientation of the hydroxyl group. According to the data in [7-9], in sulfuric acid

---

Scientific-Research Institute of Organic Intermediates and Dyes, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 805-808, June, 1974. Original article submitted March 15, 1973.

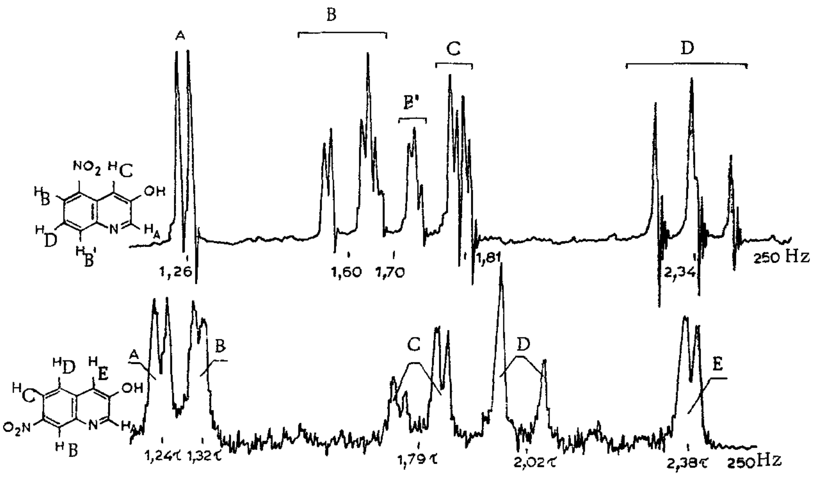


Fig. 1. PMR spectra of 5-nitro-3-hydroxyquinoline (II) and 7-nitro-3-hydroxyquinoline (III) (with hexamethyldisiloxane as the internal standard).

quinoline is nitrated as the quinolinium ion. It may be assumed that this is also valid for 3-hydroxyquinoline I: the nitration is realized exclusively in the benzene ring in conformity with the directing effect of the hydroxyl goup. In acetic acid, at least a portion of 3-hydroxyquinoline I may be present in the molecular form and may be nitrated in the most active (4) position [10].

The PMR spectra of II and III are presented in Fig. 1. Signal A in the spectrum of II is affiliated with H_2, while signal C is affiliated with H_4 [5]. The additional doublet splitting of signal C may be due to coupling of H_4 and H_8 [11]. Signal D is affiliated with H_7 and shows that the nitro group is in the 5 position when the 8 position is free. The left-hand portion of signal B corresponds to proton H_6, and the right-hand portion of signal B (B') is affiliated with H_8.

An investigation of the spectrum of III demonstrated that two isomers with a nitro group in the 6 or 7 position may correspond to this spectrum. The presence of spin–spin coupling between the B and E protons makes it possible to favor the 7-nitro isomer.

EXPERIMENTAL

The UV spectra of solution of the compounds in alcohol–ammonia (49 : 1) were recorded with an SF-8 spectrophotometer. The PMR spectra of deuterated dimethyl sulfoxide solutions were recorded with a Varian HA-100 spectrometer at 250 Hz. The chromatographs were obtained on Silufol UV-254 plates (dioxane, ammonia vapors).

5-Nitro-3-hydroxyquinoline (II) and 7-Nitro-3-hydroxyquinoline (III). A 3.36-ml (0.04 mole) sample of HNO_3 (sp. gr. 1.35) was added to 5.8 g (0.04 mole) of I in 40 ml of concentrated H_2SO_4, and the mixture was stirred at 0° for 1 h, after which it was poured over ice. Four compounds in the following order of decreasing R_f values on the chromatogram were detected in the reaction mixture: traces of I (blue luminescence in UV light), II and III (yellow luminescence), and traces of IV. The precipitate was removed by filtration and washed to neutrality with ice water to give 5.8 g (76.3%) of II with mp 230.5° (from 50% C_2H_5OH). Alkylation of the acidic filtrate to pH 2-3 with concentrated ammonium hydroxide yielded 1.63 g (21.4%) of a mixture of II and III with traces of IV. Another 0.13 g (1.7%) of the same mixture of isomers was extracted from the filtrate with butanol. A 1.76-g sample of the mixture was treated with dioxane and filtered to give 0.54 g (7.1%) of III with mp 249.7° (from aqueous alcohol). The filtrate was evaporated to dryness, and chromatographic comparison established that the residue contained 0.9 g of II (overall yield 88.2%) and 0.3 g of III (overall yield 11.2%). UV spectrum, λ_{max}, nm (log ε) II: 240 (4.40), 435 (3.75); III: 230 (4.44), 295 (3.73), 410 (4.21). Found for II: C 56.5; H 3.2; N 14.9%. For III: C 56.8; H 3.2; N 14.7%. $C_9H_6N_2O_3$. Calculated: C 56.8; H 3.2; N 14.7%.

The oxidation of 0.57 g (0.003 mole) of II in a solution of 0.2 g of KOH and 1.26 g (0.008 mole) of $KMnO_4$ in 130 ml of water at 0° gave 0.17 g of m-nitroaniline.

4-Nitroanthranilic acid [12] was isolated from the oxidation of III under similar conditions with subsequent alkaline hydrolysis of the resulting oxalylanthranilic acid.

4-Nitro-3-hydroxyquinoline (IV). A 1.4-ml (0.03 mole) sample of concentrated HNO_3 was added to 4.35 g (0.03 mole) of I in 110 ml of glacial CH_3COOH, and the precipitated I was removed by filtration and dried to give 6.14 g (98%) of product. All of this product was dissolved in 100 ml of CH_3COOH, and the solution was held at 50-60° for 10-15 min. Yellow crystals of IV [2.96 g (52%)] precipitated from the cooled solution. A total of 1.18 g of unchanged I was isolated from the filtrate by chromatography with a column filled with silica gel (elution with ammoniacal dioxane). The yield of IV, with mp 187.5-187.9° (from aqueous C_2H_5OH), based on the converted I was 69.8%. UV spectrum, λ_{max}, nm (log ε): 235 (4.43), 345 (3.48), 420 (3.55). Found: C 57.0; H 3.2; N 14.7%. $C_9H_6N_2O_3$. Calculated: C 56.8; H 3.2; N 14.7%.

4-Amino-3-hydroxyquinoline (V). A 0.6-ml (78 mmole) sample of hydrazine hydrate and 0.02 g of Raney nickel in dimethylformamide (DMF) were added to a solution of 0.5 g (0.026 mole) of IV in DMF. After 15-20 min the reaction mixture was filtered, the solvent was evaporated to dryness, and the residue was recrystallized from water to give 0.35 g (85.3%) of V with mp 119.7°. Found: N 14.7%. $C_9H_8N_2O$. Calculated: N 14.7%. The N,O-dibenzoyl derivative of V had mp 197.4-197.8° (from methanol). Found: C 75.1; H 4.3; N 7.7%. $C_{23}H_{16}N_2O_3$. Calculated: C 75.0; H 4.4; N 7.6%.

4-Chloro-3-hydroxyquinoline (VI). A 0.1-g (1.5 mmole) sample of $NaNO_2$ was added to 0.22 g (1.5 mmole) of V in 1.5 ml of concentrated HCl, after which the mixture was held at 20° for 1 h and then stirred at 60-70° for 2 h. The solution was neutralized with 2 N NaOH, and the precipitate was removed by filtration, dried, and suspended in dioxane. The insoluble portion was removed by filtration and recrystallized from water to give 0.1 g (40%) of VI with mp 202.4°. No melting-point depression was observed for a mixture of this product with a known sample obtained by the method in [13].

4,5-Dinitro-3-hydroxyquinoline (VII). A) A 0.38-g (2 mmole) sample of II was dissolved in 15 ml of CH_3COOH, and the solution was cooled and treated with 0.1 ml (2 mmole) of concentrated HNO_3. The precipitated II was removed by filtration, dried, and heated with stirring in 20 ml of CH_3COOH for 15-20 min. Cooling gave 0.13 g (26%) of crystals of VII with mp 190° (from alcohol).

B) A 2-ml sample of HNO_3 (sp. gr. 1.5) was added at −15° to 0.38 g (2 mmole) of IV in 3 ml of concentrated H_2SO_4. After 1 h, the mixture was poured over ice, and the resulting precipitate was removed by filtration, washed to neutrality, and dried to give 0.17 g (38%) of VII with mp 189.3° (from alcohol). No melting-point depression was observed for a mixture of samples of compounds obtained by methods A and B. Found: C 46.2; H 2.2; N 17.8%. $C_9H_5N_3O_5$. Calculated: C 46.0; H 2.2; N 17.9%.

LITERATURE CITED

1. J. S. Dewar and P. M. Maitlis, J. Chem. Soc., 2521 (1957).
2. K. Schofield and T. Swain, J. Chem. Soc., 1367 (1949).
3. E. Ochiai, C. Kaneko, T. Kosuge, S. Migashita, and C. Kawasaki, Chem. Pharm. Bull., Tokyo, 8, 24 (1960).
4. H. von Euler, H. Hasselquist, and D. Nomura, Ark. Kemi, 15, 283 (1960).
5. T. Nakashima and J. Suzuki, Chem. Pharm. Bull., Tokyo, 17, 2293 (1969).
6. R. Kahn, Ber., 3863 (1903).
7. K. Schofield, D. M. G. Crout, and J. R. Penton, J. Chem. Soc., B, 1254 (1971).
8. M. W. Austin, M. Brickman, J. H. Ridd, and B. V. Smith, Chem. Ind., London, 1057 (1962).
9. M. W. Austin and J. H. Ridd, J. Chem. Soc., 4204 (1963).
10. I. Gyenes, Titrations in Nonaqueous Media, Van Nostrand-Reinhold (1968).
11. J. Emsley, J. Finney, and L. Sutcliffe, High-Resolution Nuclear Magnetic Resonance Spectroscopy, Pergamon (1966).
12. P. Grammaticakis, Compt. Rend., 1585 (1961).
13. L. L. Smirnov, N. A. Andronova, V. P. Lezina, V. E. Latyshev, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 456 (1971).