SYNTHESIS AND BROMINATION OF 8-METHYLQUINOLINE-5-CARBOXYLIC ACID

I. N. Gracheva and A. I. Tochilkin

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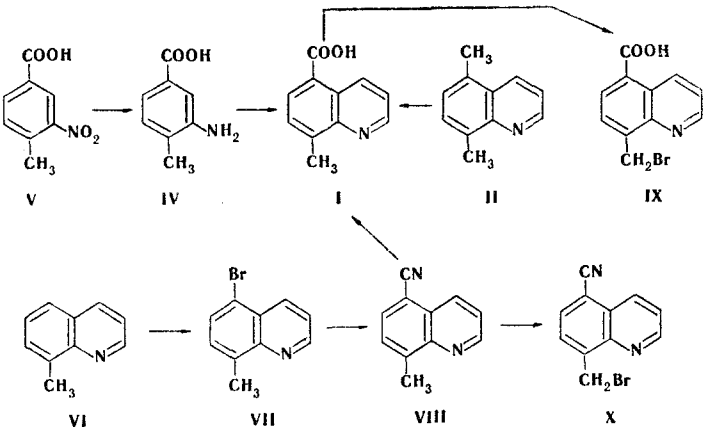
8-Methylquinoline-5-carboxylic acid was obtained by the Skraup reaction from 3-amino-p-toluic acid or by hydrolysis of 5-cyano-8-methylquinoline. The latter was synthesized by the Rosenmund–von Braun reaction from 5-bromo-8-methylquinoline, which was obtained by bromination of 8-methylquinoline in the presence of silver sulfate. Bromination in the side chain of 8-methylquinoline-5-carboxylic acid and its nitrile was studied.

Quinoline derivatives are of interest as potential inhibitors of monoamino oxidase (MAO) [1]. Quinolinecarboxylic acids may serve as the starting substances for the synthesis of certain MAO inhibitors. The present communication is devoted to the synthesis of 8-methylquinoline-5-carboxylic acid (I).



The only described synthesis of acid I consists in oxidation of 5,8-dimethylquinoline (II) with nitric or chromic acid [2, 3]. According to our data, the oxidation of dimethylquinoline II (obtained by a modified Skraup method [4]) with nitric acid [2] to quinolinecarboxylic acid I proceeds ambiguously in low yield and is not of preparative value. An attempt to selectively monobrominate quinoline II with N-bromosuccinimide to 5-bromomethyl-8-methylquinoline, which could have been converted to acid I, led only to 5,8-bis(bromomethyl)quinoline (III).

The Skraup reaction, which is widely used to obtain various acids of the quinoline series, has not been used up until now for the synthesis of acid I. We synthesized acid I by this method from 3-amino-p-toluic acid (IV), which was obtained by hydrogenation of 3-nitro-p-toluic acid (V) [5]. A considerable increase in the yield (up to 80%) in the synthesis of acid I was obtained by carrying out the reaction in 65% sulfuric acid; the yield does not exceed 15% when concentrated sulfuric acid is used. Extraction with a mixture of chloroform and dimethylformamide is effective for more nearly complete isolation of the product.

The synthesis of acid I from 8-methylquinoline (VI), bromination of which in the presence of silver sulfate, as in the bromination of quinoline [6], leads to 5-bromo-8-methylquinoline (VII) in good yield, was also found to be a convenient method for the preparation of acid I. In contrast to quinoline, polybromination is not observed in this case, and

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excess substrate is therefore not required when the bromination is carried out. Methylbromoquinoline VII is converted to 5-cyano-8-methylquinoline (VIII) in high yield by means of the Rosenmund–von Braun reaction in the presence of pyridine; when pyridine is absent, bromo derivative VII does not react with cuprous cyanide under the conditions for the preparation of 3-cyanoquinoline [7]. Hydrolysis of nitrile VIII leads to acid I, which is identical to the acid obtained via the Skraup reaction, thereby confirming the orientation in the bromination of quinoline VI under the indicated conditions.

For purposes associated with the synthesis of monoamino oxidase inhibitors it was necessary to obtain bromo-substituted derivatives of acid I and its nitrile (VIII). Bromination of acid I with N-bromosuccinimide in carbon tetrachloride, chloroform, or methyl acetate [8] proceeds very slowly and leads to 8-bromomethylquinoline-5-carboxylic acid (IX) in only low yield, evidently because of the low solubility of acid I in organic solvents. On the other hand, the bromination of nitrile VIII under similar conditions proceeds readily and leads to 5-cyano-8-bromomethylquinoline (X) in good yield.

The structures of the compounds obtained were confirmed by the IR spectra. Acid I was characterized in the form of the methyl ester and the hydrobromide. Salts with 2,4,6-trinitrobenzenesulfonic acid, which are convenient for the identification of compounds of the quinoline series, were obtained from derivatives VII and VIII.

EXPERIMENTAL

The IR spectra of KCl pellets of the compounds were obtained with a Unicam SP-1000 apparatus. The systems for thin-layer chromatography (TLC) on Silufol UV-254 were as follows: carbon tetrachloride–isopropyl alcohol (4:1) (A), benzene–acetone (5:1) (B), and benzene–ethyl acetate–acetic acid (100:50:1) (C).

3-Amino-p-toluic Acid (IV). A 3.72-g (0.02 mole) sample of acid V was hydrogenated in 20 ml of methanol in the presence of Pd black for 5 h, after which the catalyst was removed by filtration, and the filtrate was refluxed with charcoal and evaporated to give 1.4 g (48%) of acid IV with mp 164-166°C (from methanol) (mp 164-165°C [9]). The substance was homogeneous in system B.

8-Methylquinoline-5-carboxylic Acid (I). A mixture of 5 g (0.03 mole) of acid IV, 10 g (0.03 mole) of $[Fe(SO_3C_6H_4NO_2)_3 \cdot 4.5H_2O]$, 8ml (0.1 mole) of glycerol, and 50 ml of 65% H_2SO_4 was heated at 140°C for 4 h, after which it was cooled and treated with 40% aqueous NaOH to pH 3. The precipitate was separated, and the filtrate was neutralized to pH 7 and extracted with chloroform–dimethylformamide (DMF) (10:1). The extract was concentrated in vacuo at 60°C to give 5 g (80%) of acid I with mp 280°C [from DMF–alcohol (20:1)] (mp 286°C [3]). IR spectrum: 1727 cm^{-1} (COOH). The substance was homogeneous in system A. Found: C 70.0; H 4.9; N 7.8%. $C_{11}H_9NO_2$. Calculated: C 70.6; H 4.8; N 7.9%. The hydrobromide (obtained by treatment of I with hydrobromic acid) melted above 300°C. Found: C 49.4; H 3.4; Br 29.7; N 5.1%. $C_{11}H_9NO_2 \cdot HBr$. Calculated: C 49.2; H 3.7; Br 30.0; N 5.3%. The methyl ester (obtained with diazomethane in ether) had mp 51-52°C (from hexane). Found: C 72.0; H 6.6; N 6.7%. $C_{12}H_{11}NO_2$. Calculated: C 72.0; H 5.5; N 7.0%.

5,8-Dimethylquinoline (II). A mixture of 30 ml (0.2 mole) of p-xylidene, 34 ml (0.4 mole) of glycerol, 36 g (0.07 mole) of ferric m-nitrobenzenesulfonate, and 20 ml of concentrated H_2SO_4 was heated at 160-170°C for 4 h, after which it was cooled, treated with 200 ml of water, made alkaline with aqueous KOH solution, and extracted with hexane. Evaporation of the solvent gave quinoline II with bp 125-126°C (10 mm) [bp 125°C (10 mm) [10]].

Oxidation of 5,8-Dimethylquinoline. A mixture of 0.5 ml (3 mmole) of quinoline II, 0.5 ml of nitric acid (sp. gr. 1.4), and 0.5 ml of water was heated in a sealed ampul at 200°C for 15 min, after which the mixture was cooled and poured into water. The aqueous mixture was neutralized with 10% NH_4OH, the oil was separated, and the aqueous layer was acidified with acetic acid to give 24 mg (4%) of acid I, which, according to the IR spectrum and the results of TLC, was identical to the product obtained via the Skraup reaction.

5,8-Bis(bromomethyl)quinoline (III). A mixture of 5.1 g (0.03 mole) of quinoline II and 2.1 g (0.01 mole) of N-bromosuccinimide in 100 ml of carbon tetrachloride was refluxed for 5 h in the presence of benzoyl peroxide with irradiation with a 200-W lamp. The precipitate was separated, washed with water, and dried to give 2.6 g of quinoline III. Another 2.5 g of quinoline III was isolated from the filtrate to give an overall yield of

5.1 g (50%) of a product with mp 132-134°C (from benzene). The substance was homogeneous in system A. Found: C 41.7; H 3.1; N 3.7%. $C_{11}H_9Br_2N$. Calculated: C 41.9; H 2.9; N 4.5%.

5-Bromo-8-methylquinoline (VII). A 17.3-g (0.11 mole) sample of bromine was added with stirring in the course of 40 min (during which the temperature rose to 35°C) to a solution of 17 g (0.055 mole) of silver sulfate and 15.4 g (0.11 mole) of 8-methylquinoline in 90 ml of concentrated H_2SO_4, and the mixture was stirred for 30 min. It was then poured into 1200 ml of cold water, and the precipitated silver bromide was removed by filtration (90% yield). The acidic filtrate was made alkaline with aqueous KOH solution, and the precipitated product (which was initially oily) was removed by filtration and dissolved in ether. The ether solution was filtered, and the solvent was evaporated to give 20.6 g (86%) of bromo-substituted VII with mp 38-39°C (from methanol–ether) and bp 165-166°C (25 mm) (mp 37-38°C [11]). The substance was homogeneous in system C. The 2,4,6-trinitrobenzenesulfonate (obtained in methanol) had mp 280-281°C (dec.). Found: Br 15.7; N 10.9; S 6.4%. $C_{10}H_8BrN \cdot C_6H_3N_3O_9S$. Calculated: Br 15.5; N 10.9; S 6.2%.

5-Cyano-8-methylquinoline (VIII). A mixture of 11.7 g (0.07 mole) of bromoquinoline VII, 6.9 g (0.07 mole) of cuprous cyanide, and 12 ml of dry pyridine was heated for 2.5 h at 205-215°C, after which it was cooled, and the solidified pulverized reaction mixture was extracted exhaustively with ether in a Soxhlet apparatus. The solvent was removed, and the residue was sublimed twice at 0.05 mm to give 7.2 g (82%) of a product with mp 106-107°C. (from methanol). IR spectrum: 2202 cm^{-1} (CN). The substance was homogeneous in system C. Found: C 78.4; H 5.0; N 16.6%. $C_{11}H_8N_2$. Calculated: C 78.6; H 4.8; N 16.6%. The 2,4,6-trinitrobenzenesulfonate (obtained in methanol) had mp 263-265°C (dec.). Found: N 15.3; S 7.8%. $C_{11}H_8N_2 \cdot C_6H_3N_3O_9S$. Calculated: N 15.2; S 7.0%.

Hydrolysis of Nitrile VIII. A solution of 0.3 g (1.8 mmole) of nitrile VIII in 2 ml of 70% H_2SO_4 was heated at 120°C for 2 h, after which it was cooled with ice, treated carefully with 10% NH_4OH to pH 2-3, and worked up to give 0.14 g (41%) of acid I, which was purified as described above. The substance was identical to the product obtained via the Skraup reaction according to the IR spectrum and the results of TLC.

8-Bromomethylquinoline-5-carboxylic Acid (IX). A mixture of 0.2 g (1.1 mmole) of acid I and 0.2 g (1.2 mmole) of N-bromosuccinimide in 50 ml of chloroform (purified to remove alcohol) was refluxed in the presence of benzoyl peroxide with irradiation with a 200-W lamp. After 20 h, the precipitate was separated, the filtrate was evaporated, and the reaction mixture was dissolved in alcohol. The precipitated acid I was removed by filtration, and the filtrate was evaporated to give 0.03 g (10%) of quinoline IX (viscous oil). The substance was homogeneous in system A. Found: Br 30.1; N 5.8%. $C_{11}H_8BrNO_2$. Calculated: Br 31.0; N 5.3%.

5-Cyano-8-bromomethylquinoline (X). A 4-g (0.02 mole) sample of nitrile VIII was brominated for 2 h by means of 4.2 g (0.02 mole) of N-bromosuccinimide in 50 ml of carbon tetrachloride, as described for IX. The succinimide was separated, and the filtrate was evaporated to give 4 g (67%) of bromonitrile X with mp 96-98°C (from chloroform–ether). Found: C 72.8; H 3.5; N 13.4%. $C_{11}H_7BrN_2$. Calculated: C 72.7; H 3.3; N 13.4%.

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