SYNTHESIS OF SOME BIFUNCTIONAL DERIVATIVES OF 8-METHYLQUINOLINE-5-CARBOXYLIC ACID

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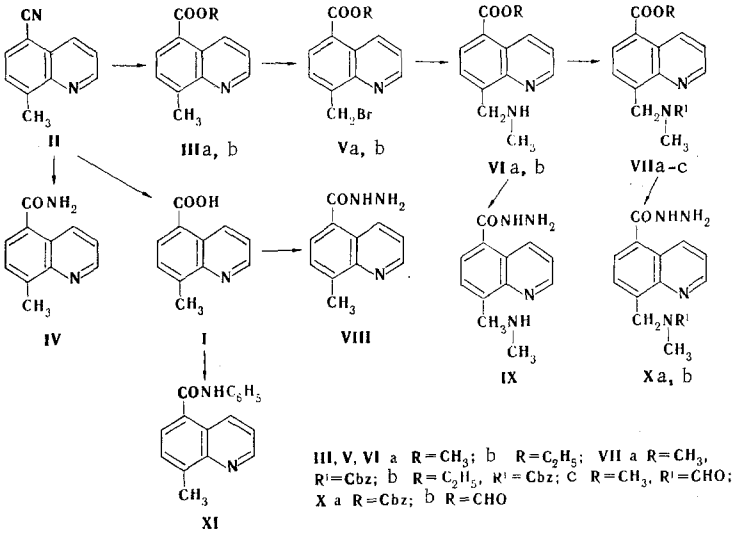
Derivatives of 8-methylquinoline-5-carboxylic acid were synthesized. Alcoholysis of 8-methyl-5-cyanoquinoline gave methyl and ethyl 8-methylquinoline-5-carboxylates, which were converted to the corresponding 8-bromomethyl derivatives. The latter were used for the introduction of a methylamino group and the synthesis of N-acyl derivatives. The hydrazide, amide, and anilide of 8-methylquinoline-5-carboxylic acid were obtained as model compounds.

We have previously described [1] a synthesis of 8-methylquinoline-5-carboxylic acid (I) that made it accessible and expanded the synthetic possibilities for its utilization. However, the chemical transformations of both this acid and its other isomers associated with the introduction of an amino group in the side chain and the simultaneous transformation of the carboxy function have not been studied up until now. At the same time, bifunctional derivatives of this sort may be valuable, particularly in the synthesis of monoamine oxidase inhibitors.

The present communication is devoted to the synthesis of some nitrogen-containing derivatives of 8-methylquinoline-5-carboxylic acid, particularly derivatives involving amino substitution at the methyl group that simultaneously contain a potentially activated carboxy function.

As the starting compound we used the previously synthesized 5-cyano-8-methylquinoline (II) [1]:



Methyl and ethyl 8-methylquinoline-5-carboxylates (IIIa, b) were obtained by alcoholysis of nitrile II in the presence of sulfuric acid. Nitrile II is readily converted to 8-methylquinoline-5-carboxamide (IV) by the action of potassium hydroxide in tert-butyl alcohol by the method in [2]. Bromination of esters IIIa, b with N-bromosuccinimide (NBS) leads to methyl and ethyl 8-bromomethylquinoline-5-carboxylates (Va, b) in high yields; the latter react with methylamine to give methyl and ethyl 8-(N-methyl)aminomethylquinoline-5-carboxylates (VIa, b), which were difficult to isolate in the base form and were characterized in the hydrochloride form.

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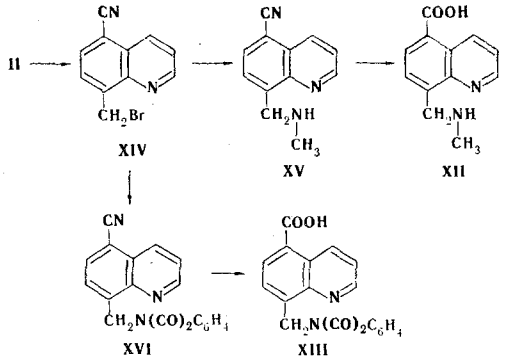
N-Carbobenzoxylation and N-formylation were used to protect the amino group in the subsequent transformations of the carboxy group. Amino esters VIa, b are converted by the Schotten–Baumann method to methyl and ethyl 8-(N-methyl-N-carbobenzoxy)aminomethylquinoline-5-carboxylates (VIIa, b), and amine VI is formylated with a mixture of formic acid and acetic anhydride to give methyl 8-(N-methyl-N-formyl)-aminomethylquinoline-5-carboxylate (VIIc). Hydrazinolysis of esters III, VI, and VII leads to 8-methyl-, 8-(N-methyl)aminomethyl-, 8-(N-methyl-N-carbobenzoxy)aminomethyl-, and 8-(N-methyl-N-formyl)amino-methylquinoline-5-carboxylic acid hydrazides (VIII-Xa, b). In the case of the preparation of the anilide (XI) and hydrazide (VIII) of acid I we demonstrated the possibility of activation of the carboxy group for this group of compounds by means of N,N'-carbonyldiimidazole [3]. The synthesis of amino acids with a free carboxy group, viz., 8-(N-methyl)aminomethylquinoline-5-carboxylic acid (XII) and 8-(N-phthaloyl)aminomethylquinoline-5-carboxylic acid (XIII) was realized via the following scheme:



5-Cyano-8-bromomethylquinoline (XIV) [1] is converted to 8-(N-methyl)aminomethyl-5-cyanoquinoline (XV) by reaction with methylamine, while the reaction of bromide XIV with potassium phthalimide gives 8(N-phthaloyl)aminomethyl-5-cyanoquinoline (XVI), which is hydrolyzed by 70% sulfuric acid at 120°C to acids XII and XIII, respectively. The described transformations proceed quite smoothly and can probably also be used in the case of other methylquinolinecarboxylic acids.

The structures of all of the compounds obtained were confirmed by the results of elementary analysis and the IR spectra.

EXPERIMENTAL

The IR spectra of KCl pellets of the compounds were recorded with a Unicam SP-1000 spectrometer. The systems for thin-layer chromatography (TLC) on Silufol UV-254 were chloroform–methanol–25% NH_4OH–water (A), benzene–ethyl acetate–acetic acid (100:50:1) (B), carbon tetrachloride–isopropyl alcohol (9:1) (C), and acetonitrile–25% NH_4OH (8:1) (D).

Methyl and Ethyl 8-Methylquinoline-5-carboxylates (IIIa, b). A 3-g (20 mmole) sample of nitrile I was refluxed in a mixture of 33 ml of methanol and 15 ml of concentrated H_2SO_4. After 48 h, the mixture was cooled and treated with 200 ml of water, neutralized with 20% NaOH solution, and extracted with chloroform. The extract was dried with Na_2SO_4, and the solvent was evaporated to give 2 g (55%) of IIIa with mp 51-52°C (from hexane). IR spectrum: 1720 cm^{-1} (C=O). The substance was homogeneous in system C. Found: C 72.0; H 5.7; N 6.7%. $C_{12}H_{11}NO_2$. Calculated: C 71.6; H 5.5; N 7.0%. Similarly, nitrile II gave ester IIIb (48%) with mp 53-54°C (from chloroform). IR spectrum: 1720 cm^{-1} (C=O). The substance was homogeneous in system C. Found: C 64.5; H 7.0; N 5.8%. $C_{13}H_{13}NO_2 \cdot 1.5H_2O$.* Calculated: C 64.8; H 6.6; N 5.9%.

8-Methylquinoline-5-carboxamide (IV). An 840-mg (5 mmole) sample of nitrile II was refluxed in a mixture of 25 ml of tert-butyl alcohol and 5 ml of methanol in the presence of 1 g (17 mmole) of KOH. After 2 h, a saturated solution of NaCl was added, and the precipitate was separated, washed with 50 ml of water, and dried over P_2O_5 to give 600 mg (64%) of a product with mp 232-233°C (from ethanol). IR spectrum: 1680 (CONH); 3180, 3375 cm^{-1} (NH_2). The substance was homogeneous in system D. Found: C 71.0; H 5.5; N 15.2%. $C_{11}H_{10}N_2O$. Calculated: C 71.0; H 5.4; N 15.0%.

* The percentage of water here and subsequently was determined by drying the derivatives at 80°C (10 mm) over P_2O_5. Drying the substances under these conditions for analysis was undesirable, since it led to partial resinification; drying in a desiccator did not remove the bonded water.

Methyl and Ethyl 8-Bromomethylquinolinecarboxylates (Va, b). A 2-g (10 mmole) sample of ester IIIa was refluxed with 1.95 g (11 mmole) of N-bromosuccinimide (NBS) in 40 ml of CCl_4 in the presence of a catalytic amount of benzoyl peroxide with irradiation with a 200-W lamp. The precipitated succinimide was separated, the filtrate was evaporated, and the residue was washed with ethanol and dried to give 1.97 g (70%) of ester IVa with mp 118-119°C (from ethanol). The substance was homogeneous in system B. Found: C 51.2; H 3.2; Br 28.6; N 5.2%. $C_{12}H_{10}BrNO_2$. Calculated: C 51.5; H 3.4; Br 28.5; N 5.0%. Ester Vb, with mp 61-63°C (from ethanol), was similarly obtained in 75% yield. The substance was homogeneous in system B. Found: C 53.2; H 4.1; N 4.7%. $C_{13}H_{12}BrNO_2$. Calculated: C 53.1; H 4.1; N 4.7%.

Hydrochlorides of Methyl and Ethyl 8-(N-Methyl)aminomethylquinoline-5-carboxylates (VIa, b). A mixture of 1.7 g (6 mmole) of bromide Va was added in the course of an hour to 40 ml of a 30% methanol solution of methylamine. After 30 min, the mixture was evaporated, 25 ml of 25% NH_4OH was added, and the mixture was extracted with chloroform. The organic layer was dried with Na_2SO_4, the solvent was evaporated, and the residue was subjected to preparative TLC on silica gel in system A to give 0.6 g (45%) of amino ester VIa (R_f 0.5), which was converted to the hydrochloride by treatment with HCl in dioxane. The hydrochloride had mp 119-121°C (from ethanol). IR spectrum: 3440 cm^{-1} (NH). The substance was homogeneous in system A. Found: C 50.2; H 6.0; N 9.0%. $C_{13}H_{14}N_2O_4 \cdot 2HCl \cdot 0.5H_2O$. Calculated: C 50.0; H 5.5; N 9.0%. Amino ester VIb was similarly obtained in 40% yield and was converted to the hydrochloride as described above. The hydrochloride had mp 191-192°C (from ethanol). IR spectrum: 3440 cm^{-1} (NH). The substance was homogeneous in system A. Found: C 53.6; H 5.8; N 9.2%. $C_{14}H_{16}N_2O_2 \cdot 2HCl$. Calculated: C 53.1; H 6.1; N 8.9%.

Methyl and Ethyl 8-(N-Methyl-N-carbobenzoxy)methylaminoquinoline-5-carboxylates (VIIa, b). A mixture of 960 mg (3 mmole) of ester VIa in 10 ml of water and 5 ml of chloroform was treated alternately with ice cooling in the course of 30 min with 0.7 ml (4 mmole) of carbobenzoxy chloride and 200 mg (6 mmole) of magnesium oxide. The mixture was stirred with cooling for 30 min and at ~20°C for 1 h, after which it was treated with 0.1 ml of pyridine. After 5 min, the mixture was acidified to pH 2-3 with dilute HCl, and the organic layer was separated and diluted with chloroform. The mixture was washed with 0.1 N HCl and a 4% solution of sodium bicarbonate. The solvent was evaporated, and the residue was dissolved in absolute ethanol. Treatment with ethanol was repeated three times to give 1.2 g (79%) of VIIa (a viscous oil). IR spectrum: 1738 cm^{-1} (OCON). The substance was homogeneous in system B. Found: C 68.4; H 5.3; N 7.9%. $C_{21}H_{20}N_2O_4$. Calculated: C 69.2; H 5.5; N 7.7%. Similar treatment of ester VIb gave VIIb (an oil) in 56.6% yield. IR spectrum: 1738 cm^{-1} (OCON). The substance was homogeneous in system B. Found: C 70.0; H 6.2; N 8.9%. $C_{22}H_{22}N_2O_4$. Calculated: C 69.8; H 6.8; N 8.9%.

Methyl 8-(N-Methyl-N-formyl)aminomethylquinoline-5-carboxylate (VIIc). A solution of 400 mg (1.6 mmole) of ester VIa in a mixture of 2 ml of formic acid and 2 ml of acetic anhydride was stirred at 20°C, after which the solvent was evaporated, and the residue was dried over NaOH to give 200 mg (45%) of VIIc (a viscous oil). IR spectrum: 1667 cm^{-1} (CON). The substance was homogeneous in system A. Found: C 64.7; H5.5; N 11.1%. $C_{14}H_{14}N_2O_3$. Calculated: C65.1; H 5.5; N 10.9%.

8-Methylquinoline-5-carboxylic Acid Hydrazide (VIII). A) A mixture of 250 mg (1.2 mmole) of ester IIIb, 3 ml of hydrazine hydrate, and 3 ml of absolute ethanol was refluxed for 4-6 h, after which the solution was concentrated, and 100 mg (42%) of hydrazide VIII with mp 187-190°C (from ethanol) was separated. IR spectrum: 1638 (CONH); 3225, 3300 cm^{-1} (NH_2). The substance was homogeneous in system A. Found: C 65.4; H 5.6; N 21.1%. $C_{11}H_{11}N_3O$. Calculated: C 65.7; H 5.5; N 20.9%.

B) A mixture of 50 mg (0.25 mmole) of acid I and 50 mg (0.31 mmole) of N,N'-carbonyldiimidazole in 1.5 ml of dry THF was maintained at 40-50°C for 10 min and at ~20°C for 15 min. After CO_2 evolution ceased, 0.15 ml of 85% hydrazine hydrate was added to the solution, and the mixture was stirred at ~20°C for 1.5 h. It was then evaporated, and the residue was treated with 2 ml of water to give 15 mg (30%) of hydrazide VIII with mp 188-190°C (from ethanol), which was identical to the substance obtained by method A.

The following compounds were obtained under the conditions of experiment A: 8-(N-methyl)aminomethylquinoline-5-carboxylic acid hydrazide (IX) [51% (a viscous oil). IR spectrum: 3300 cm^{-1} (NH_2). The substance was homogeneous in system A. Found: 64.5; H 7.0; N 5.8%. $C_{12}H_{14}N_4O \cdot 1.5H_2O$. Calculated: C 65.0; H 6.9; N 6.7%], 8-(N-methyl-N-carbobenzoxy)methylaminoquinoline-5-carboxylic acid hydrazide (Xa) [80% (a viscous oil). Found: C 66.5; H 6.3; N 15.2%. $C_{20}H_{20}N_4O_3$. Calculated: C 65.9; H 5.5; N 15.4%], and 8-(N-methyl-N-formyl)aminomethylquinoline-5-carboxylic acid hydrazide (Xb) [50% (a viscous oil). Found: C 54.5; H 5.5; N 19.4%. $C_{13}H_{14}N_4O_2 \cdot 1.5H_2O$. Calculated: C 54.9; H 5.9; N 19.7%].

8-Methylquinoline-5-carboxylic Acid Anilide (XI). Acid I [95 mg (0.5 mmole)] in 2 ml of dry THF was treated at 20°C with 125 mg (0.77 mole) of N,N'-carbonyldiimidazole. After 2 h, 0.1 ml (1 mmole) of aniline

was added, and the mixture was allowed to stand at 20°C for 24 h. It was then filtered, and the filtrate was evaporated. The product was crystallized by trituration with water to give 80 mg (61%) of anilide XI with mp 210-211°C (from ethanol). The substance was homogeneous in system B. Found: N 10.6%. $C_{17}H_{14}N_2O$. Calculated N 10.7%.

8-(N-Methyl)aminomethyl-5-cyanoquinoline (XV). This compound was obtained in 63% yield (an oil) by the method used to prepare amine V. The substance was homogeneous in system A. Found: C 72.0; H 5.8; N 20.7%. $C_{12}H_{11}N_3O \cdot 0.25H_2O$. Calculated: C 71.5; H 6.4; N 20.6%.

8-(N-Phthaloyl)aminomethyl-5-cyanoquinoline (XVI). A solution of 300 mg (1.2 mmole) of bromide XIV in dimethylformamide (DMF) was treated for 30 min at ~20°C with 255 mg (1.2 mmole) of potassium phthalimide. Water (50 ml) was added, and the precipitate was separated to give 300 mg (87%) of nitrile XVI with mp 183-184°C (from ethanol). IR spectrum: 2202 (C≡N); 1717, 1766 cm^{-1} (CONCO). Found: C 72.8; H 3.5; N 13.5%. $C_{19}H_{11}N_3O_2$. Calculated: C 72.8; H 3.5; N 13.4%.

8-(N-Methyl)aminomethylquinoline-5-carboxylic Acid (XII). A mixture of 600 mg (3 mmole) of nitrile XV and 2 ml of 70% H_2SO_4 was heated at 120°C for 2 h, after which it was poured into water with cooling and stirred with Dowex 2×8 (OH^-) resin to pH 5. The resin was separated, the aqueous solution was concentrated, and 540 mg (82%) of acid XIV with mp 210-214°C (from ethanol) was separated. IR spectrum: 1718 cm^{-1} (COOH). The substance was homogeneous in system A. Found: C 45.7; H 5.4; N 9.6%. $C_{12}H_{12}N_2O_2 \cdot H_2SO_4$. Calculated: C 45.9; H 4.6; N 8.9%.

8-(N-Phthaloyl)aminomethylquinoline-5-carboxylic Acid (XIII). A mixture of 1 g (3.2 mmole) of phthaloyl derivative XVI was heated at 120°C in 10 ml of 70% H_2SO_4. After 2 h, the mixture was cooled with ice and treated with NH_4OH to pH 2. The precipitate was separated, washed with water and dried over P_2O_5 to give 820 mg (78%) of acid XIII* with mp 224-228°C (from ethanol). IR spectrum: 1766 (CONCO) and 1718 cm^{-1} (COOH + CONCO). The substance was homogeneous in systems A and D. Found: C 68.7; H 3.7; N 8.2%. $C_{19}H_{12}N_2O_4$. Calculated: C 68.0; H 3.6; N 8.4%.

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* Hydrolysis of the phthalimide group occurs under more severe conditions (150°C); this is confirmed by disappearance of the band at 1766 cm^{-1}.