# DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

## SYNTHESIS OF DERIVATIVES OF 2-FLUOROALKYL-6,7-DIFLUOROQUINOLONE-3-CARBOXYLIC ACID

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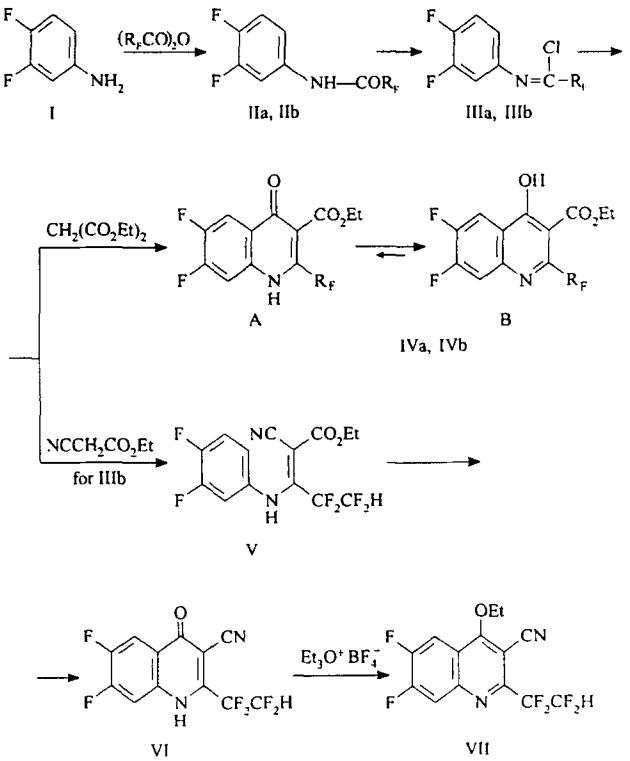
Antibiotics of the fluoroquinolone series [1 – 7] occupy an important place among the antimicrobial chemical preparations. Their high antimicrobial activity and broad spectrum of action explain the interest of researchers in the synthesis of fluoroquinolones with modified structures and in new quinolone-like compounds capable of inhibiting DNA gyrase [8].

Among the numerous derivatives of fluoroquinolone-3-carboxylic acids, the majority belong to 7-piperazinyl-substituted quinolones having various substituents in positions 1, 5, and 8 [3 – 5]. Much less attention has been paid to the introduction of substituents into position 2 or [a]annelation of heterocycles in the quinolone system. However, there is some evidence that this approach may also be fruitful [4]. The present article is devoted to the synthesis of 2-fluoroalkyl-6,7-difluoroquinolones that serve as key intermediates in the schemes used to obtain antibacterial compounds of the fluoroquinolone series.

The method proposed for obtaining 2-fluoroalkyl-6,7-difluoroquinolones is based on the acylation of 3,4-difluoroaniline (I) with anhydrides of poly(fluoroalkanecarboxylic) acids, followed by conversion of the resulting anilides (IIa, IIb) into iminochlorides (IIIa, IIIb) with the aid of phosphorus pentachloride. Iminochlorides IIIa and IIIb are introduced into reaction with malonic ester in the presence of sodium hydride and, without isolating the intermediates, closed by prolonged heating to obtain esters of 4-quinolone-3-carboxylic acid (IVa, IVb). According to the data of $^1$H NMR spectroscopy, the latter esters may occur in the form of two prototropic tautomers A and B (with predominance of the 4-hydroxy form of B).




A similar reaction takes place between iminochloride IIIb and cyanoacetic ester and leads to quinolone (VI) via an isolated intermediate V. The $^1$H NMR spectrum of VI gives evidence of a single tautomeric form (presumably oxo-isomer), as may be judged by the signal of the NH group at 5.12 ppm. However, a comparison with the spectra of compounds IVa and IVb (measured in deuterochloroform) is incorrect, because compound VI is poorly soluble in $CDCl_3$ and the spectrum was obtained only in DMSO-$d_6$. The alkylation of quinolone VI with triethyloxonium tetrafluoroborate led exclusively to a 4-ethoxy derivative (VII).

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The proposed structures of compounds II – VII were reliably confirmed by elemental analyses and the results of $^1H$ and $^{19}F$ NMR measurements.

The results of preliminary testing of the activity of the synthesized compounds with respect to conventional bacterial strains showed no pronounced effects.

## EXPERIMENTAL CHEMICAL PART

The NMR spectra were measured on a Bruker WP-80 spectrometer, operated at 80 MHz, using deuterochloroform or DMSO-$d_6$ as solvents. The IR absorption spectra were recorded on an UR-20 spectrophotometer (Germany) using samples prepared as nujol mulls.

**N-(3,4-Difluorophenyl)amide of trifluoroacetic acid (IIa).** To a solution of 23 g (0.11 mole) of trifluoroacetic acid anhydride in 200 ml of dry ethyl ether was added dropwise, on cooling and stirring, a mixture of 12.9 g (0.1 mole) of 3,4-dufluoroaniline [9] and 11 g (0.11 mole) of triethylamine in 50 ml of dry ether. The reaction mass was stirred for 3 h and then the solvent was evaporated. The residue was treated with 100 ml of water. The precipitate was separated by filtration and recrystallized from aqueous ethanol to obtain 18.0 g (80%) of N-(3,4-difluorophenyl)amide of trifluoroacetic acid (IIa); m.p., 105 – 106°C; $C_8H_4F_5NO$; IR spectrum ($\nu_{max}$, $cm^{-1}$): 1680, 1740 ($CONH_2$), 3260, 3320 (NH).

**N-(3,4-Difluorophenyl)amide of 2,2,3,3-tetrafluoropropionic acid (IIb)** was obtained by a similar procedure from 12.9 g (0.1 mole) of 3,4-difluoroaniline and 30.1 g (0.11 mole) of 2,2,3,3-tetrafluoropropionic acid anhydride. Yield: 22.9 g (89%); m.p., 73 – 74°C (aqueous ethanol); $C_9H_5F_6NO$; IR spectrum ($\nu_{max}$, $cm^{-1}$): 1630, 1710 ($CONH_2$), 3260, 3310 (NH).

**N-(3,4-Difluorophenyl)trifluoromethyliminochloride (IIIa).** A mixture of 22.5 g (0.1 mole) of N-(3,4-difluorophenyl)amide of trifluoroacetic acid (IIa) and 21 g (0.1 mole) of finely ground phosphorus pentachloride was placed in a round-bottom 500-ml flask and slowly heated to 60 – 70°C, at which temperature an exothermal reaction begins in the system. After completion of the reaction, the mass was boiled at 150 – 160°C for 48 h on a Wood's alloy bath. The resulting phosphorus oxychloride was distilled by heating on a water bath in vacuum, and the residue was dissolved in chloroform and washed with water. Then the chloroform solution was dried over calcined calcium chloride, the chloroform was distilled off, and the residue was fractionated in vacuum to collect a fraction boiling at 65 – 75°C and a pressure of 3 Torr. N-(3,4-Difluorophenyl)trifluoromethyliminochloride (IIIa) is obtained in the form of a colorless oil with a yield of 11.5 g (46%); $C_8H_3F_5ClN$.

Iminochloride IIIb was obtained by an analogous procedure at with yield of 52%; $C_9H_4F_6ClN$.

**Ethyl ester of 2-trifluoromethyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (IVa).** To a suspension of 1.92 g (0.04 mole) of sodium hydride in 100 ml of dry ethyl ether was added dropwise a solution of 3.2 g (0.02 mole) of malonic ester in 20 ml of dry ether and the mixture was stirred until hydrogen completely ceases to evolve. Then a solution of 5.5 g (0.02 mole) of iminochloride IIIa in 15 ml of dry ether was slowly added in drops, and the reaction mass was stirred for 12 h and treated with water (50 ml) and 2% aqueous HCl (50 ml). The ester layer was separated and dried over calcined magnesium sulfate, the ether distilled off, and the residue heated at 205 – 210°C for 30 min on a Wood's alloy bath. Then the reaction mass was cooled, dissolved in chloroform, boiled with charcoal, filtered, and extracted with hexane to obtain 2.18 g (34%) of the ethyl ester of 2-trifluoromethyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (IVa); m.p., 159 – 160°C; $C_{13}H_8F_5NO_3$; $^1H$ NMR spectrum in deuterochloroform (δ, ppm): 12.69 (s, 1H, OH), 7.62 – 8.12 (m, 2H, Ar), 4.1 – 4.4 (2q, 2H, $OC_2H_5$), 1.0 – 1.4 (2t, 3H, $CH_3$); IR spectrum ($\nu_{max}$, $cm^{-1}$): 1640 (C=O), 1740 ($COOC_2H_5$), 3260 (NH). The content of form B was 78%, as determined by the ratio of integral intensities of two quadrupole signals due to $OCH_2$ protons of the ester group.

**The ethyl ester of 2-(1,1,2,2-tetrafluoromethyl)-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxyacid (IVb)** was obtained by a similar procedure with a yield of 62%; m.p., 169 – 170°C; $C_{14}H_9F_6NO_3$; $^1H$ NMR spectrum in deuterochloroform (δ, ppm): 13.01 (s, 1H, OH), 9.73 (NH), 7.62 – 8.16 (m, 2H, Ar), 6.86 (m, $CF_2CF_2H$), 4.1 – 4.4 (2q, 2H, $OC_2H_5$), 1.0 – 1.4 (2t, 3H, $CH_3$); IR spectrum ($\nu_{max}$, $cm^{-1}$): 1620 (C=O), 1740 ($COOC_2H_5$), 3250 (NH). The content of form B was 60%, as determined by the ratio of integral intensities of two quadrupole signals due to $OCH_2$ protons of the ester group.

**Ethyl ester of 2-cyano-3-(1,1,2,2-tetrafluoroethyl)-3-(3,4-difluorophenylamino)acrylic acid (V).** To a suspension of 2 g (0.083 mole) of sodium hydride in 200 ml of dry ethyl ether was slowly added a solution of 4.52 g (0.044 mole) of cyanoacetic ester in 20 ml of dry ether and the mixture was stirred for 30 min. Then a solution of 11.2 g (0.04 mole) of iminochloride IIIb in 30 ml of dry ether was added, and the reaction mass was stirred on heating for 10 h. Upon cooling, the reaction mass was treated with water and aqueous HCl to a weak acidic reaction. The organic layer was separated, dried over calcined magnesium sulfate, the ether distilled off, and the residue recrystallized from a chloroform – hexane mixture to obtain 6.58 g (48%) of the ethyl ester of 2-cyano-3-(1,1,2,2-tetrafluoroethyl)-3-(3,4-difluorophenylamino)acrylic acid (V); m.p., 68 – 69°C; $C_{14}H_{10}F_6N_2O_2$.

**3-Cyano-2-(1,1,2,2-tetrafluoroethyl)-6,7-difluoro-4-oxo-1,4-dihydroquinoline (VI).** The ethyl ester of 2-cyano-3-(1,1,2,2-tetrafluoroethyl)-3-(3,4-difluorophenylamino)acrylic acid (V) (3.5 g, 0.01 mole) was heated to 210 – 215°C and treated at this temperature until solidification (for about 1 h). Upon cooling, the reaction mass was dissolved in an acetone – chloroform mixture (1 : 1), boiled with charcoal, and filtered. Then hexane was added to the filtrate until complete

precipitation of the product VI. Yield, 1.99 g (68%; m.p., 250°C; $C_{12}H_4F_6N_2O$; $^1H$ NMR spectrum in DMSO-$d_6$ (δ, ppm): 7.54 – 8.15 (m, 2H, Ar), 7.02 (m, $CF_2CF_2H$), 5.12 (s, NH); IR spectrum ($\nu_{max}$, $cm^{-1}$): 1620 (C=O), 2250 (CN), 3230 (NH).

**6,7-Difluoro-2-(1,1,2,2-tetrafluoroethyl)-3-cyano-4-ethoxyquinoline (VII).** To a solution of 3.6 g (0.01 mole) of 3-cyano-2-(1,1,2,2-tetrafluoroethyl)-6,7-difluoro-4-oxo-1,4 -dihydroquinoline (VI) in 20 ml methylene chloride was added on stirring at room temperature 5.3 g (0.027 mole) of triethyloxonium tetrafluoroborate and the mixture was stirred for 5 h. Then the reaction mixture was treated with water (2 × 30 ml) and the organic layer was dried over calcined sodium sulfate. Finally, methylene chloride was distilled off on a rotor evaporator to obtain 2.73 g (82%) of 6,7-difluoro-2-(1,1,2,2-tetrafluoroethyl)-3-cyano-4-ethoxyquinoline (VII); m.p., 190°C (with decomp.); $C_{14}H_8F_6N_2O$; $^1H$ NMR spectrum in deuterochloroform (δ, ppm): 7.77 – 8.11 (m, 2H, Ar), 6.67 (m, $CF_2CF_2H$), 4.87 (q, 2H, $CH_2O$), 1.64 (t, 3H, $CH_3$); IR spectrum ($\nu_{max}$, $cm^{-1}$): 1620 (C=O), 2250 (CN), 3230 (NH).

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