# Synthesis of *N*-substituted 2-(5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids

*G. A. Obanin,* A. S. Fokin, Ya. V. Burgart, O. V. Ryzhkov, Z. E. Skryabina, V. I. Saloutin, and O. N. Chupakhin*

*Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, 20 ul S. Kovalevskoy, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343 2) 74 5954. E-mail: saloutin@ios.uran.ru*

Methods for the synthesis of the earlier unknown *N*-substituted 2-(5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids and their esters from copper chelate of ethyl pentafluorobenzoylpyruvate were developed. The structure of intermediate ethyl 4-(R-amino)-2-oxo-3-pentafluorobenzoylbut-3-enoates is discussed.

**Key words:** ethyl pentafluorobenzoylpyruvate, ethyl 4-(R-amino)-2-oxo-3-pentafluorobenzoylbut-3-enoates, 3-ethoxalyl-5,6,7,8-tetrafluoroquinolin-4-ones, *N*-substituted 2-(5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids.

Substituted fluoroquinolone-3-carboxylic acids are objects of close examination because of their unique antibacterial properties and the medical use of a variety of their derivatives, namely, fluoroquinolone antibiotics.[1,2] The ways of structural modification of these compounds are far from being exhausted to the present.

In the present work, *N*-substituted 2-(5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids and their esters were obtained for the first time, and efficient methods for their synthesis were developed.

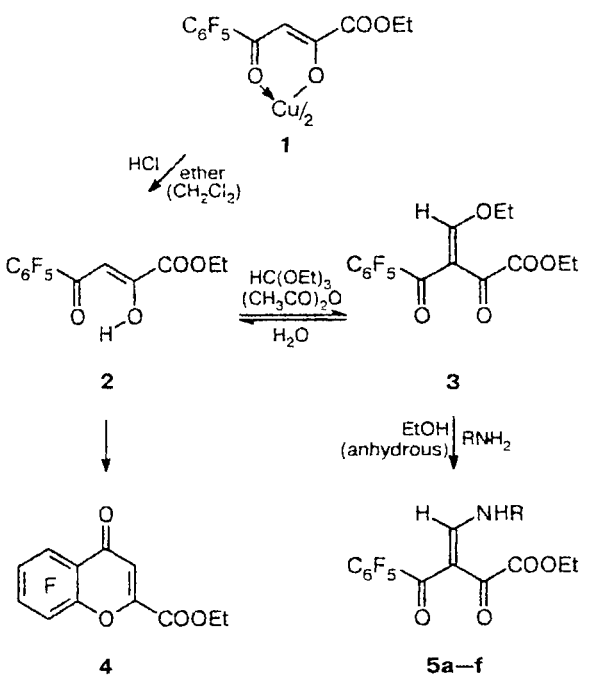
One of the known ways of preparing such systems, *viz.*, fluorine-containing 2-(1-alkyl-4-oxo-1,4-dihydroquinoline)carboxylic acids, is the Gould—Jacobs method based on alkyl fluorobenzoylacetates.[1]

Copper chelate of ethyl pentafluorobenzoylpyruvate **1** was chosen as the starting compound for the synthesis of fluoroquinolone-3-glyoxylic acids. At the first stage, chelate **1** was decomposed with dry gaseous HCl in an anhydrous solvent (ether or dichloromethane). Then, the resulting ethyl pentafluorobenzoylpyruvate (**2**) was treated (without additional purification) with ethyl formate in the presence of acetic anhydride to give ethoxymethylene derivative **3** (Scheme 1).

Copper chelate **1** as the starting compound was preferred to a free ligand (as is the case in the synthesis of fluoroquinolone-3-carboxylic acids[1]) because ester **2** tends to transform into 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**4**) even in the presence of trace amounts of water.

It turned out that ethoxymethylene derivative **3**, unlike fluorobenzoylacetic analogs,[3] is unstable and can easily hydrolyze to give back ester **2** with its subsequent transformation into the most stable chromone **4**. This is confirmed by our check experiment: refluxing ester **3** in water directly resulted in chromone **4** in good yield

**Scheme 1**




R = Et (**a**), *cyclo*-Pr (**b**), *o*-$MeC_6H_4$ (**c**), H (**d**), Me (**e**), $C_6H_{13}$ (**f**)

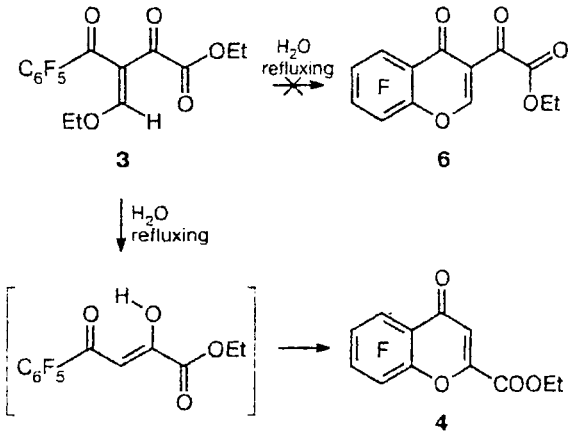
(Scheme 2). Interestingly, in this case, the expected 3-ethoxalyl-5,6,7,8-tetrafluorochromone **6** is not formed, whereas an ethoxymethylene derivative of alkyl pentafluorobenzoylacetate undergoes, under similar conditions, characteristic cyclization into 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromone.[4] Moreover, all our attempts

Published in *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 7, pp. 1234—1239, July, 2000.

1066-5285/00/4907-1231 $25.00 

to synthesize 3-ethoxalyl-5,6,7,8-tetrafluorochromone **6** failed.

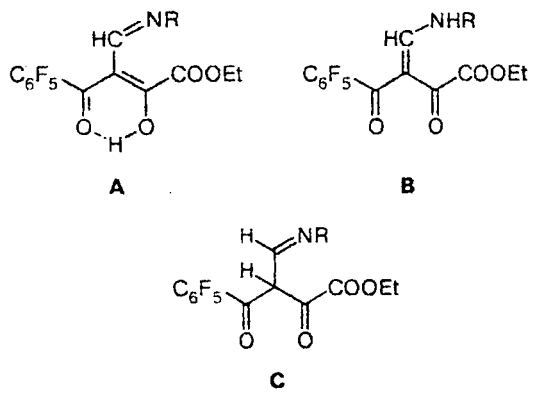
**Scheme 2**



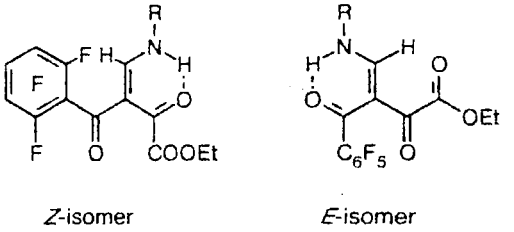

To decrease the probability of formation of by-products and increase the yield of the target compounds, unstable esters **2** and **3** were not isolated from the reaction mixture. In some cases, chromone **4** was formed (Scheme 1); it was filtered off following the dilution of the reaction mixture with anhydrous ethanol.

The reactions of an ethoxymethylene derivative of ethyl pentafluorobenzoylpyruvate **3** with various amines (ammonia; methyl-, ethyl-, cyclopropyl-, and *n*-hexylamines; and *o*-toluidine) afforded acyclic precursors of quinolones, namely, ethyl 4-(R-amino)-2-oxo-3-pentafluorobenzoylbut-3-enoates (**5a—f**) (Scheme 1), which are rather stable compounds. They were isolated and characterized by IR and NMR spectroscopy and elemental analysis (Table 1).

Compounds **5a—f** are characterized by keto-enol and amino-imine tautomerism and hence can exist either as one of three tautomeric forms (enol-imine **A**, keto-amine **B**, or keto-imine **C**) or as their mixture.




Note that keto-amine tautomer **B**, in turn, can exist in the form of *Z*- and *E*-isomers.




Analysis of the IR spectra of products **5a—f** suggests that these compounds in the solid state exist as keto-amine tautomers **B**, because, first, the range of absorption of the α-carbonyl groups (1660—1640 $cm^{-1}$) is more characteristic of the carbonyl group conjugated with other C=C and C=O bonds (structure **B**) than of an enolized carbonyl[5] (structure **A**); second, intense absorption bands in the range 3380—3170 $cm^{-1}$ can be assigned to the NH stretching vibrations (tautomer **B**) rather than to enol OH ones.

The existence of compounds **5a—f** in solution in the form of keto-amine tautomers **B** was concluded from the analysis of their $^1H$ NMR spectra. Thus, the doublet character of a signal for a methine proton at δ 7.54—8.46 rules out the presence of enol-imine tautomer **A**. The chemical shift of the second doublet (δ 9.97—13.51) is characteristic of the NH proton involved in intramolecular hydrogen bonding. There is no doubt that these two facts indicate keto-amine tautomer **B**. In addition, the presence of two sets of signals (corresponding to *Z*- and *E*-isomers) in the NMR spectra of **5a—f** is also evidence in favor of tautomer **B**.

Thus, the $^1H$ NMR spectra ($CDCl_3$) of products **5a—f** show two sets of signals in the ratio 1 : 1, which correspond to the *Z*- and *E*-isomers of these compounds. The $^{19}F$ NMR spectra ($CDCl_3$) of esters **5a—f** also contain two sets of signals characteristic of the pentafluorobenzoyl group, *viz.*, six multiplets in the ratio 2 : 2 : 1 : 1 : 2 : 2.

*Z*- and *E*-Isomers differ in the character of the signal of the methine proton. Thus, in the case of the *Z*-isomer, this signal is observed as a doublet of triplets with $J_{H-H}$ = 8.9—14.3 Hz and $J_{H-F}$ ≈ 1.5 Hz, which is due to the coupling with the NH proton and *ortho*-fluorine atoms of the aromatic substituent. In the *E*-isomer, such a coupling is impossible. Other signals cannot be assigned to one or the other isomer.

We showed that compounds **5a—f**, when heated in the presence of a base in a dry aprotic solvent (toluene or chloroform), undergo intramolecular cyclization owing to nucleophilic substitution of an amino group for the *ortho*-fluorine atom in the aromatic ring, which results in the corresponding 3-ethoxalyl-5,6,7,8-tetrafluoroquinolones (**7a—f**) (Scheme 3, Table 1). Triethylamine was used as a base.

**Table 1.** Main characteristics of ethyl 4-(R-amino)-2-oxo-3-pentafluorobenzoylbut-3-enoates **5a—f** and 5,6,7,8-tetrafluoroquinolones **7a—f**, **8a—c**, and **9**

| Compound | M.p. /°C | Yield (%) | Found / Calculated (%) C | H | F | N | Molecular formula | IR, ν/cm$^{-1}$ | NMR (CDCl$_3$, δ, *J*/Hz) $^1$H | $^{19}$F |
|---|---|---|---|---|---|---|---|---|---|---|
| **5a*** | 158—159 | 45 | 49.21<br>49.31 | 3.39<br>3.31 | 25.99<br>26.00 | 3.91<br>3.83 | $C_{15}H_{12}F_5NO_4$ | 3200 (NH); 1730 (COOEt); 1650 (C=O); 1620 ($C_6F_5C$=O); 1590 (C=C) | 1.26—1.55 (m, 6 H, $CH_3$); 3.32—4.10 (m, 2 H, $CH_2$); 4.23, 4.27 (both q, 2 H, $CH_2$); 7.61 (d.t, 0.5 H, CH, $J_{H-H}$ = 13.8, $J_{H-F}$ = 1.5; *Z*-isomer); 8.28 (d, 0.5 H, CH, $J_{H-H}$ = 13.8; *E*-isomer); 10.86, 11.23 (both d, 1 H, NH, $J_{H-H}$ = 13.8) | −0.09, 2.12 (both m, 2 F); 7.94, 10.84 (both m, 1 F); 18.69, 21.84 (both m, 2 F) |
| **5b*** | 143 | 39 | 51.15<br>50.94 | 3.19<br>3.25 | 25.09<br>25.18 | 3.83<br>3.71 | $C_{16}H_{12}F_5NO_4$ | 3170 (NH); 1730 (COOEt); 1650 (C=O); 1610 ($C_6F_5C$=O); 1590 (C=C) | 0.78—1.08 (m, 4 H, $CH_2$); 1.34 (t, 3 H, $CH_3$, $J$ = 7.3); 2.86—3.25 (m, 1 H, CH); 4.24, 4.28 (both q, 2 H, $CH_2$, $J$ = 7.3); 7.68 (d.t, 0.5 H, CH, $J_{H-H}$ = 14.1, $J_{H-F}$ = 1.5; *Z*-isomer); 8.37 (d, 0.5 H, CH, $J_{H-H}$ = 14.1; *E*-isomer); 10.84, 11.26 (both br.d, 1 H, NH, $J$ = 14.1) | 0.09, 2.21 (both m, 2 F); 8.01, 11.13 (both m, 1 F); 18.63, 21.87 (both m, 1 F) |
| **5c*** | 134—135 | 60 | 56.11<br>56.21 | 3.07<br>3.30 | 22.26<br>22.23 | 3.39<br>3.28 | $C_{20}H_{14}F_5NO_4$ | 3380 (NH); 1735 (COOEt); 1640 (C=O); 1615 ($C_6F_5C$=O); 1590 (C=C) | 1.36, 1.38 (both t, 3 H, $CH_3$, $J$ = 7.1); 2.42, 2.48 (both s, 3 H, $CH_3$); 4.26, 4.32 (both q, 2 H, $CH_2$, $J$ = 7.1); 7.03—7.40 (m, 4 H, $C_6H_4$); 7.66 (d.t, 0.5 H, CH, $J_{H-H}$ = 14.1, $J_{H-F}$ = 1.5; *Z*-isomer); 8.46 (d, 0.5 H, CH, $J$ =13.6; *E*-isomer); 12.65, 13.51 (both br.d, 1 H, NH, $J$ =13.6) | 0.36, 2.44 (both m, 2 F); 8.77, 11.67 (both m, 1 F); 19.41, 22.39 (both m, 2 F) |
| **5d*** | 197 | 32 | 46.44<br>46.30 | 2.39<br>2.39 | 28.31<br>28.17 | 4.16<br>4.15 | $C_{13}H_8F_5NO_4$ | 3380, 3255 (NH); 1720 (COOEt); 1660 (C=O); 1625 ($C_6F_5C$=O); 1610 (C=C) | 1.32, 1.35 (both t, 3 H, $CH_3$, $J$ = 7.0); 4.19, 4.30 (both t, 2 H, $CH_2$, $J$ = 7.0); 7.38 (br.s, 1 H, NH); 7.67, 7.76 (both br.dd, 1 H, CH, $J$ = 8.9); 9.97, 10.09 (both br.s, 1 NH; $J$ = 8.9) | 0.04, 2.32 (both m, 2 F); 8.42, 11.32 (both m, 1 F); 18.56, 21.62 (both m, 2 F) |
| **5e*** | 224 | 18 | 48.10<br>47.88 | 2.81<br>2.87 | 27.16<br>27.05 | 3.89<br>3.99 | $C_{14}H_{10}F_5NO_4$ | 3200 (NH); 1735, 1720 (COOEt); 1660, 1650 (C=O); 1610 ($C_6F_5C$=O); 1595 (C=C) | 1.34 (br.t, 3 H, $CH_3$, $J$ = 7.3); 3.29 (d.d, 3 H, $CH_3$, $J$ = 5.2); 4.20, 4.27 (both q, 2 H, $CH_2$, $J$ = 7.3); 7.54 (d.t, 0.5 H, CH, $J_{H-H}$ = 14.3, $J_{H-F}$ = 1.5; *Z*-isomer); 8.25 (d, 0.5 H, CH, $J_{H-H}$ = 14.3; *E*-isomer); 10.75, 11.13 (both br.s, 1 H, NH) | 0.07, 2.16 (both m, 2 F); 7.97, 10.85 (both m, 1 F); 18.64, 21.8 (both m, 2 F) |
| **5f*** | 104—106 | 37 | 54.13<br>54.16 | 4.75<br>4.78 | 22.67<br>22.54 | 3.49<br>3.32 | $C_{19}H_{20}F_5NO_4$ | 3200 (NH); 1740 (COOEt); 1650 (C=O); 1610 ($C_6F_5C$=O); 1600 (C=C) | 0.85—1.00 (m, 2 H, $CH_2$); 1.23—1.89 (m, 9 H, $CH_3$, $CH_2$); 3.32—3.62 (m, 2 H, $CH_2$); 4.25 (m, 2 H, $CH_2$, $J$ = 8.2); 7.55 (d.t, 0.5 H, CH, $J_{H-H}$ = 13.3, $J_{H-F}$ = 1.5; *Z*-isomer); 8.25 (d, 1 H, CH, $J_{H-H}$ = 13.3; *E*-isomer); 10.87, 11.20 (both br.s, 1 H, NH, $J_{H-H}$ = 13.3) | 0.05, 2.08 (both m, 2 F); 7.92, 10.81 (both m, 1 F); 18.75, 21.88 (both m, 2 F) |

(*To be continued*)

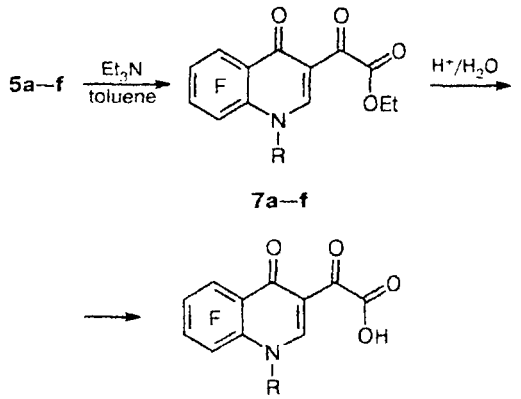
**Table 1.** (*Continued*)

| Compound | M.p. /°C | Yield (%) | Found / Calculated (%) C | H | F | N | Molecular formula | IR, $\nu/cm^{-1}$ | NMR ($CDCl_3$, δ, *J*/Hz) $^1H$ | $^{19}F$ |
|---|---|---|---|---|---|---|---|---|---|---|
| **7a** | 168—170 | 91 | 52.28<br>52.18 | 3.06<br>3.21 | 21.65<br>22.01 | 3.94<br>4.06 | $C_{15}H_{11}F_4NO_4$ | 3045 (CH); 1735 (COOEt); 1660 (C=O); 1640 (C=O-ring); 1610 (C=C) | 1.39 (t, 3 H, $CH_3$, *J* = 7.3); 1.57 (d.t, 3 H, $CH_3$, *J* = 7.0); 4.31—4.58 (m, 4 H, $CH_2$); 8.28 (s, 1 H, CH) | 2.67 (m, 1 F); 14.31 (m, 2 F); 20.45 (m, 1 F) |
| **7b** | 209—210 | 74 | 53.81<br>53.79 | 3.10<br>3.10 | 21.40<br>21.27 | 3.78<br>3.92 | $C_{16}H_{11}F_4NO_4$ | 3030 (CH); 1730 (COOEt); 1665 (C=O); 1630 (C=O-ring); 1605 (C=C) | 0.78—0.93 (m, 7 H, $CH_3$, $CH_2$); 4.07—4.27 (m, 1 H, CH); 4.38 (q, 2 H, $CH_2$, *J* = 7.0); 8.44 (s, 1 H, CH) | 4.57 (m, 1 F); 15.61 (m, 1 F); 17.50 (m, 1 F); 22.44 (m, 1 F) |
| **7c** | 197 | 75 | 58.75<br>58.98 | 3.19<br>3.22 | 18.75<br>18.66 | 3.30<br>3.44 | $C_{20}H_{13}F_4NO_4$ | 3045 (CH); 1740 (COOEt); 1650 (C=O); 1640 (C=O-ring); 1600 (C=C) | 1.31 (t, 3 H, $CH_3$, *J* = 7.4); 2.15 s (3 H, $CH_3$); 4.34 (q, 2 H, $CH_2$, *J* = 7.4); 7.32—7.74 (m, 4 H, $C_6H_4$); 8.34 (s, 1 H, CH) | 6.34 (m, 1 F); 29.23—29.89 (m, 2 F); 40.74 (m, 1 F) |
| **7d** | 235—237 | 63 | 49.35<br>49.23 | 2.06<br>2.22 | 23.84<br>23.96 | 4.19<br>4.42 | $C_{13}H_7F_4NO_4$ | 3395 (NH); 3060, 3040 (CH); 1735 (COOEt); 1660 (C=O); 1635 (C=O-ring) | 1.30 (t, 3 H, $CH_3$, *J* = 7.0); 4.31 (q, 2 H, $CH_2$, *J* = 7.0); 8.44 (s, 1 H, CH); 13.24 (br.s, 1 H, NH) | 1.17 (m, 1 F); 9.27 (m, 1 F); 12.61 (m, 1 F); 19.63 (m, 1 F) |
| **7e** | 173—175 | 72 | 50.89<br>50.77 | 2.91<br>2.74 | 22.80<br>22.94 | 4.48<br>4.23 | $C_{14}H_9F_4NO_4$ | 3030 (CH); 1725 (COOEt); 1665 (C=O); 1635 (C=O-ring); 1605 (C=C) | 1.40 (t, 3 H, $CH_3$, *J* = 7.0); 4.25 (d, 3 H, $CH_3$); 4.44 (q, 2 H, $CH_2$, *J* = 7.0); 8.21 s (1 H, CH) | 5.05 (m, 1 F); 13.53 (m, 1 F); 15.69 (m, 1 F); 23.24 (m, 1 F) |
| **7f** | 175 | 85 | 56.92<br>56.86 | 4.79<br>4.77 | 18.84<br>18.93 | 3.20<br>3.49 | $C_{19}H_{19}F_4NO_4$ | 3050 (CH); 1735 (COOEt); 1660 (C=O); 1645 (C=O-ring); 1605 (C=C) | 0.82—1.05 (m, 2 H, $CH_2$); 1.09—1.65 (m, 9 H, $CH_3$, 2 $CH_2$); 1.75—2.02 (m, 2 H, $CH_2$); 4.27—4.52 (m, 4 H, 2 $CH_2$); 8.25 (d, 1 H, CH) | 4.37 (m, 1 F); 13.25 (m, 1 F); 15.69 (m, 1 F); 23.13 (m, 1 F) |
| **8a** | 225—226 | 72 | 49.18<br>49.23 | 2.05<br>2.22 | 24.02<br>23.97 | 4.23<br>4.41 | $C_{13}H_7F_4NO_4$ | 1735 (COOH); 1670 (C=O); 1620 (C=O-ring); 1590 (C=C) | 1.44 (t, 3 H, $CH_3$, *J* = 7.0); 1.29 (s, OH); 4.51 (m, 1 H, $CH_2$, *J* = 7.0); 8.68 (s, 1 H, CH) | 2.67 (m, 1 F); 13.85—14.77 (m, 2 F); 20.45 (m, 1 F) |
| **8b** | 240 | 94 | 51.21<br>51.08 | 2.13<br>2.14 | 23.17<br>23.08 | 4.21<br>4.25 | $C_{14}H_7F_4NO_4$ | 1740 (COOH); 1680 (C=O-ring); 1620 (C=O); 1590 (C=C) | 1.14—1.21 (m, 4 H, $CH_2$); 1.29 (s, OH); 2.94—3.12 (m, 1 H, CH); 8.50 (s, 1 H, CH) | 2.70 (m, 1 F); 13.85 (m, 1 F); 18.88—19.84 (m, 2 F) |
| **8c** | 230—232 | 93 | 57.22<br>57.01 | 2.31<br>2.39 | 19.89<br>20.04 | 3.91<br>3.69 | $C_{18}H_9F_4NO_4$ | 1710 (COOH); 1690 (C=O); 1640 (C=O-ring); 1590 (C=C) | 2.15 (s, 3 H, $CH_3$); 4.07 (br.s, 1 H, OH); 7.48 (br.s, 4 H, $C_6H_4$); 8.27 (s, 1 H, CH) | 20.30 (m, 1 F); 14.61 (m, 2 F); 2.88 (m, 1 F) |
| **9** | 198—199 | 70 | 61.20<br>61.06 | 5.59<br>5.35 | 16.82<br>16.80 | 6.10<br>6.19 | $C_{23}H_{24}F_4N_2O_3$ | 3285 (NH); 3070 (CH); 1715 (C=ONH); 1675 (C=O); 1645 (C=O-ring); 1595 (C=C) | 1.24—2.04 (m, 20 H, $CH_2$); 4.55 (m, 2 H, CH); 6.24 (s, 1 H, CH); 7.96 (br.s, 1 H, NH) | −4.21 (m, 1 F); 1.86 (m, 1 F); 11.58 (m, 1 F); 18.31 (m, 1 F) |

* The $^1H$ and $^{19}F$ NMR spectra of compounds **5a—f** contain two sets of signals with the integral intensity ratio ≈1 : 1, which correspond to a mixture of *Z*- and *E*-isomers.

The cyclization rate depends on the reaction temperature. Thus, in boiling chloroform (b.p. 61 °C), the reaction is completed over 1.5—2 h, while in boiling toluene (b.p. 110 °C) it takes only 5—10 min. The course of the reaction was monitored by TLC.

**Scheme 3**



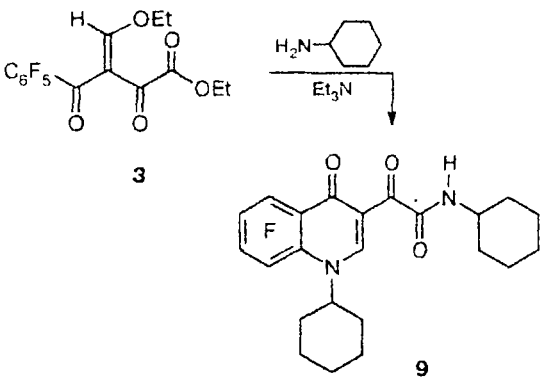

**7a—f**

**8a—c**

R = Et (**a**), cyclopropyl (**b**), *o*-$MeC_6H_4$ (**c**), H (**d**), Me (**e**), $C_6H_{13}$ (**f**).

It is noteworthy that our attempt to simplify the procedure for the synthesis of 3-ethoxalylquinolones **7**, *e.g.*, by eliminating the stage of isolation of acyclic aminomethylene derivative **5** (in the reaction with cyclohexylamine as an example), resulted in the formation of quinolone-3-glyoxylamide (**9**) rather than the expected ester (Scheme 4, Table 1). Hence, the reaction of ester **3** with cyclohexylamine in the presence of triethylamine mainly affords amide **9** in good yield, which is caused by addition of two molecules of cyclohexylamine with simultaneous cyclization into quinolone.

**Scheme 4**




**3** **9**

When refluxed in an aqueous medium with a mixture of sulfuric and acetic acids for 30 min, esters **7a—c** hydrolyze to give the corresponding fluoroquinolone-3-glyoxylic acids **8a—c** (Scheme 3, Table 1).

The obtained *N*-substituted 2-(5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids and their esters are promising not only from the viewpoint of their potential biological activity, but also as polyfunctional compounds suitable for various subsequent transformations. Intermediate ethyl 4-(R-amino)-2-oxo-3-pentafluorobenzoylbut-3-enoates are of undeniable theoretical interest.

## Experimental

IR spectra were recorded on a Specord 75 IR spectrometer (400—4000 $cm^{-1}$, Vaseline oil). $^1H$ NMR spectra were recorded on a Tesla BS-567 A spectrometer (80 MHz) with reference to $SiMe_4$. $^{19}F$ NMR spectra were recorded on a Tesla BS-587 A spectrometer (75 MHz) with $C_6F_6$ as a standard. Elemental analysis was performed on a Carlo Erba CHNS-O EA 1108 instrument.

Copper chelate of ethyl pentafluorobenzoylpyruvate **1** was prepared according to the known procedure.[4]

**Ethyl 4-ethylamino-2-oxo-3-(pentafluorobenzoyl)but-3-enoate (5a), ethyl 4-cyclopropylamino-2-oxo-3-(pentafluorobenzoyl)but-3-enoate (5b), ethyl 4-(2-methylphenylamino)-2-oxo-3-(pentafluorobenzoyl)but-3-enoate (5c), ethyl 4-amino-2-oxo-3-(pentafluorobenzoyl)but-3-enoate (5d), ethyl 4-methylamino-2-oxo-3-(pentafluorobenzoyl)but-3-enoate (5e), ethyl 4-hexylamino-2-oxo-3-(pentafluorobenzoyl)but-3-enoate (5f), and *N*-cyclohexyl-3-(1-cyclohexyl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinoline)glyoxylamide (9) (general procedure).** Dry HCl was bubbled with stirring through a solution of copper chelate **1** (10 g, 29.3 mmol) in 100 mL of dry diethyl ether until the green reaction mixture turned colorless. The ether was removed on a water bath. Acetic anhydride (6.64 mL, 78.2 mmol) and ethyl orthoformate (7.32 mL, 43.8 mmol) were then added, and the resulting solution was refluxed for 2 h. The excess of the reagents was removed *in vacuo*.

**Compounds 5a,d,e.** The residue was dissolved in 100 mL of anhydrous ethanol. Gaseous methylamine, ethylamine, or ammonia was bubbled through the solution for 10 min, and the precipitate that formed was filtered off and recrystallized from methanol.

**Compounds 5b,c,f.** The residue was dissolved in 60 mL of anhydrous ethanol. Cyclopropylamine, *o*-toluidine, or hexylamine (29.3 mmol) in 20 mL of anhydrous methanol was added. The reaction mixture was heated to the boiling point and cooled to ~20 °C. The precipitate that formed was filtered off and recrystallized from methanol.

**Amide 9.** The residue was dissolved in 60 mL of anhydrous ethanol, and cyclohexylamine (11.63 g, 117.3 mmol) was added. The reaction mixture was refluxed for 2 h and, after addition of triethylamine (8.9 g, 88 mmol), for an additional 2 h and then cooled. The precipitate that formed was filtered off and recrystallized from methanol to give product **9** (9.29 g) (see Table 1).

**1-Ethyl-5,6,7,8-tetrafluoro- (7a), 1-cyclopropyl-5,6,7,8-tetrafluoro- (7b), 5,6,7,8-tetrafluoro-1-(2-methylphenyl)- (7c), 5,6,7,8-tetrafluoro- (7d), 5,6,7,8-tetrafluoro-1-methyl- (7e), and 3-ethoxalyl-5,6,7,8-tetrafluoro-1-hexyl-1,4-dihydroquinolin-4-one (7f) (general procedure).** Triethylamine (2.53 g, 15.0 mmol) was added to a solution of compound **5** (5.0 mmol) in 30 mL of dry toluene. The reaction mixture was refluxed for

15 min, cooled, and washed with 5% HCl and distilled water to pH ~7. The toluene solution was dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was recrystallized from methanol.

**2-(1-Ethyl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)- (8a), 2-(1-cyclopropyl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)- (8b), and 2-(5,6,7,8-tetrafluoro-1-(2-methylphenyl)-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acid (8c) (general procedure).** A mixture of distilled water (3.5 mL), conc. AcOH (4.6 mL), and conc. $H_2SO_4$ (0.6 mL) was added to 3-ethoxalylquinolone **7a—c** (2.0 mmol). The reaction mixture was refluxed for 30 min, then diluted with 10 mL of distilled water, and cooled to ~20 °C. The precipitate that formed was filtered off and washed with cold methanol.

The physicochemical constants and yields of the compounds obtained are given in Table 1.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 00-03-32767a).

## References

1. G. A. Mokrushina, S. G. Alekseev, V. N. Charushin, and O. N. Chupakhin, *Zh. Vses. Khim. O-va im. D. I. Mendeleeva*, 1991, 447 [*Mendeleev Chem. J.*, 1991 (Engl. Transl.)].
2. N. Ishikawa, *Fluorine Compounds, Synthesis and Application*, Kodansha, Tokyo, 1979.
3. V. I. Saloutin, I. T. Bazyl', Z. E. Skryabina, and O. N. Chupakhin, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 362 [*Russ. Chem. Bull.*, 1993, **42**, 858 (Engl. Transl.)].
4. V. I. Saloutin, Z. E. Skryabina, I. T. Bazyl', S. G. Perevalov, and O. N. Chupakhin, *Zh. Org. Khim.*, 1994, **30**, 1225 [*Russ. J. Org. Chem.*, 1994, **30**, 1288 (Engl. Transl.)]; V. I. Saloutin, Z. E. Skryabina, I. T. Bazyl', P. N. Kondrat'ev, and O. N. Chupakhin, *J. Fluor. Chem.*, 1994, **69**, 126.
5. L. A. Kazitsyna and N. B. Kupletskaya, *Primenenie UF-, IK-, YaMR- i mass-spektroskopii v organicheskoi khimii* [*Application of UV, IR, NMR, and Mass Spectroscopy in Organic Chemistry*], Moscow State University, Moscow, 1979, 236 pp. (in Russian).

*Received November 4, 1999;*
*in revised form March 1, 2000*