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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

3-Methylidene-2,4-dioxo-4-pentafluorophenylbutanoates in the Synthesis of Heterocycles

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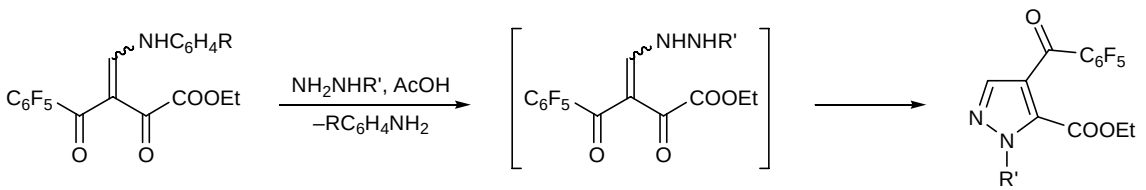
Abstract—3-Ethoxy- and 3-arylaminomethylidene-2,4-dioxo-4-pentafluorophenylbutanoates undergo cyclization by the action of hydrazine hydrate and phenylhydrazine to give ethyl 4-pentafluorobenzoylpyrazole-5-carboxylates. The reaction of 3-ethoxymethylidene-2,4-dioxo-4-pentafluorophenylbutanoate with *o*-phenylenediamine leads to formation of 3-[2-(2-aminophenylamino)-1-pentafluorobenzoylethenyl]-1,2-dihydroquinoxalin-2-one. 3-Arylaminomethylidene-2,4-dioxo-4-pentafluorophenylbutanoates react with *o*-phenylenediamine to afford 3-(1-aryl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)-1,2-dihydroquinoxalin-2-ones and/or 3-(2-arylamino-1-pentafluorobenzoylethenyl)-1,2-dihydroquinoxalin-2-ones.

Ethyl 3-methylidene-2,4-dioxo-4-pentafluorophenylbutanoates are formed as intermediate products in the synthesis of 2-[1-alkyl(aryl)-4-oxo-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-3-yl]-2-oxoacetic acids from ethyl 3-pentafluorobenzoyl-2-oxoacetate [1, 2]; these compounds attract interest as both final products and polyfunctional building blocks for the preparation of various heterocyclic systems. Unlike parent ethyl 3-pentafluorobenzoyl-2-oxopropionate (**I**), 3-methylidene-2,4-dioxo-4-pentafluorophenylbutanoates possess four electrophilic reaction centers: γ-carbonyl (pentafluorobenzoyl) group, α-carbonyl group, ethoxycarbonyl fragment, and activated double C=C bond, which should give rise to increased number of reaction fluxes and new competing reaction paths.

In the present work we examined transformations of ethyl 3-ethoxymethylidene- and 3-arylaminomethylidene-2,4-dioxo-4-pentafluorophenylbutanoates **II** and **III** with hydrazine hydrate, phenylhydrazine, and *o*-phenylenediamine. Ethyl 3-arylaminomethylidene-2,4-dioxo-4-pentafluorophenylbutanoates **IIIa**–**IIIc** were found to react with hydrazines to afford ethyl 4-pentafluorobenzoylpyrazole-5-carboxylates **IVa** and **IVb** in good yields (Scheme 1). Compounds **IVa** and **IVb** are likely to be formed as a result of consecutive transformations including substitution of the arylamino group at the double C=C bond by hydrazine and subsequent intramolecular cyclization of intermediate **A** via condensation of the amino group at the α-carbonyl group.

Presumably, the first stage is rate-determining for the whole process, for the reaction rate strongly depends on the nature of the arylamino fragment in the initial ester. The complete conversion of ester **IIIa** into

Scheme 1.



IIIa–**IIIc** **A** **IVa**, **IVb** (56–75%)

III, R = H (**a**), 2-Me (**b**), 4-MeO (**c**); **IV**, R' = H (**a**), Ph (**b**).

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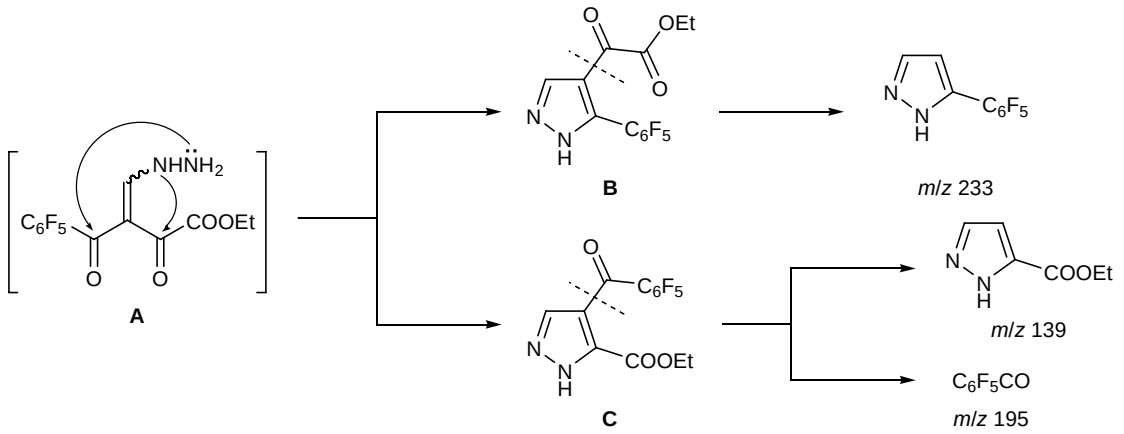
Scheme 2.



pyrazole **IVa** requires 2 h at room temperature, while analogous transformation of ester **IIIb** is complete in 48 h. This is consistent with published data [3], according to which the rate-determining stage in acid-catalyzed A_NE reactions is the addition stage [3]. Electrophilicity of the C=C bond in molecule **IIIb** is reduced (as compared to **IIIa**) due to the presence of *o*-methylphenylamino group, and the rate of addition of hydrazine decreases.

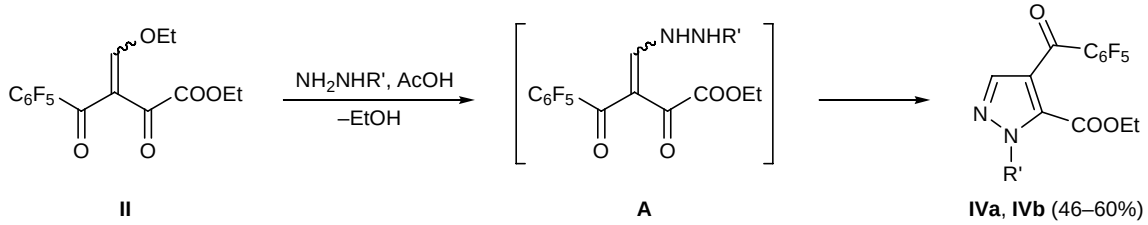
Two paths of intramolecular attack by the NHR' group are possible in intermediate ethyl 3-hydrazinomethylidene-2,4-dioxo-4-pentafluorophenylbutanoate (**A**). One of these involves the α-carbonyl group, and the other, γ-carbonyl group. As a result, isomeric pyrazoles **B** and **C** may be obtained (Scheme 2). Structure **C** was assigned on the basis of the mass spectral data. The mass spectrum of pyrazole **IVa** contained strong fragment ion peaks arising from decomposition of the molecular ion at the C–C bond connecting the pyrazole ring and pentafluorobenzoyl group (*m*/*z* 139, I = 100.0% $[M - COC_6F_5]^+$, *m*/*z* 195, I = 44.51% $[C_6F_5CO]^+$), while no pentafluorophenylpyrazole ion peak (*m*/*z* 233) was present; the latter could be formed by decomposition of alternative structure **B** (Scheme 2).

Pyrazoles **IVa** and **IVb** can also be obtained from 3-ethoxymethylidene-2,4-dioxo-4-pentafluorophenylbutanoate (**II**). The reactions of ester **II** with hydrazine hydrate and phenylhydrazine gave products whose physical properties and spectral parameters were almost identical to those of pyrazoles **IVa** and **IVb**. Presumably, these reactions also involve addition of hydrazine molecule at the C=C bond of the substrate with elimination of ethanol, followed by intramolecular cyclization of intermediate **A** at the α-carbonyl group (Scheme 3). Undoubtedly, the latter procedure for the synthesis of pyrazoles **IV** is more advantageous since 3-arylamino-methylidene-2,4-dioxo-4-pentafluorophenylbutanoates **III** are usually prepared from 3-ethoxymethylidene-substituted analog **II** and the corresponding arylamine [1] while the latter is liberated in the synthesis of heterocycles **IV** from ester **III**.

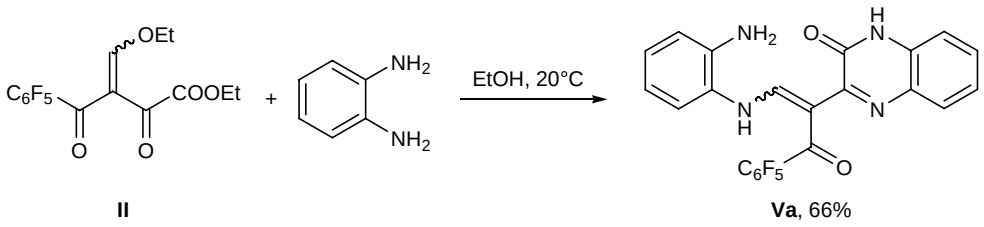
It is seen that the behavior of 3-methylidene-2,4-dioxobutanoates **II** and **III** toward hydrazines differs from the behavior of their precursor, pentafluorobenzoylpyruvate **I**, though in both cases the products are heterocyclic compounds of the pyrazole series. However, these products are formed following different heterocyclization paths: cyclocondensation of pentafluorobenzoylpyruvate **I** with hydrazines involves the β-dicarbonyl fragment to give ethyl 5-pentafluorophenylpyrazole-3-carboxylates [4], while 3-methylidene-2,4-dioxobutanoates **II** and **III** undergo cyclization with participation of the α-oxovinyl moiety.

We also examined reactions of ethyl 3-methylidene-2,4-dioxo-4-pentafluorophenylbutanoates **II** and **III** with *o*-phenylenediamine. The reaction of 3-ethoxy-

Scheme 3.



Scheme 4.



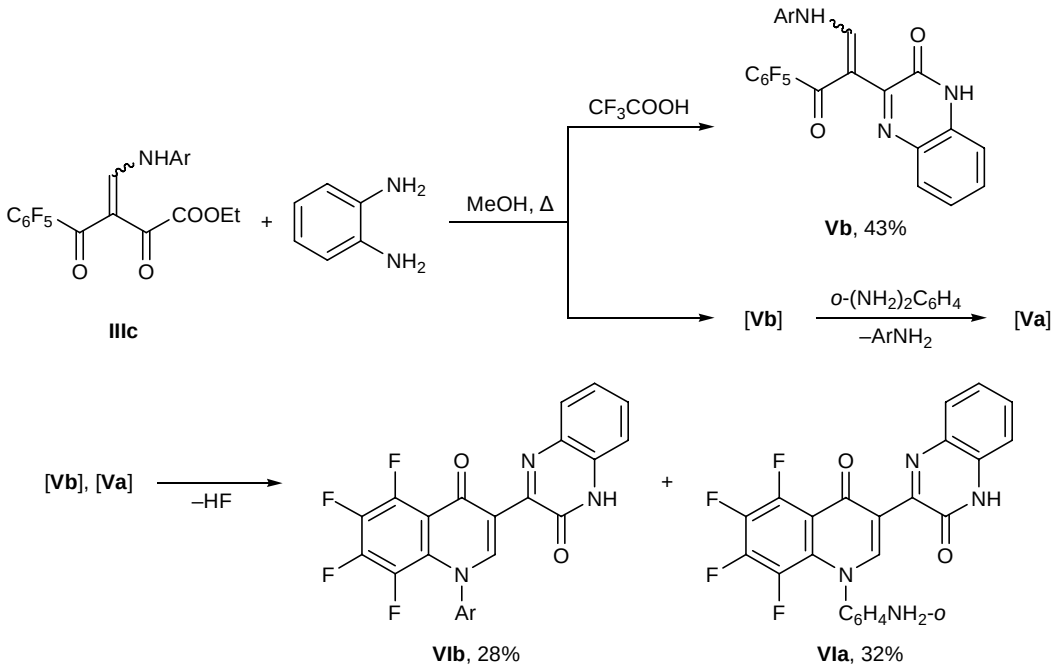
II **Va**, 66%

methylidene derivative **II** with *o*-phenylenediamine was also accompanied by replacement of the ethoxy group by nucleophile. However, the subsequent condensation of the second *o*-phenylenediamine molecule at the α-oxo ester fragment led to formation of 3-substituted 1,2-dihydroquinoxalin-2-one **Va** (Scheme 4). Unlike ester **II**, ethyl 3-arylaminomethylidene-2,4-dioxo-4-pentafluorophenylbutanoates **III**, depending on the conditions, reacted with *o*-phenylenediamine either at the α-oxo ester fragment to give 3-substituted 1,2-dihydroquinoxalin-2-ones **V** (like pentafluorobenzoylpyruvate **I** and its derivatives [5]) or with concomitant transamination of the arylamino group at the C=C bond by the second nucleophile molecule. 1,2-Dihydroquinoxalin-2-one **Vb** was obtained from ester **IIIc** and *o*-phenylenediamine in methanol in the presence of a catalytic amount of trifluoroacetic acid (Scheme 5). In the absence of acid catalyst, cyclocondensation at the α-oxo ester moiety was followed by replacement of the arylamino group at the C=C bond by *o*-phenylenediamine residue. Here, the conditions favoring transamination promote cyclization of quinoxalinones **Va** and **Vb** to the corresponding 3-quinolylquinoxalinones **VIa** and **VIb** via intramolecular nucleophilic substitution of fluorine atom in the *ortho* position of the pentafluorophenyl group by the amino group in the methylidene fragment. As a result, compounds **VIa** and **VIb** were isolated as final products (Scheme 5).

According to the NMR data, quinoxalinones **Va** and **Vb**, like their acyclic precursors (esters **III**), in solution exist as mixtures of *Z* and *E* isomers [1] differing by orientation of the amino group with respect to the C=C bond.

Thus we have shown that ethyl 3-methylidene-2,4-dioxo-4-pentafluorophenylbutanoates **II** and **III** exhibit a different reactivity toward difunctional nucleophiles, as compared to ethyl 3-pentafluorobenzoyl-2-

Scheme 5.



IIIc **Vb**, 43% **VIb**, 28% **VIa**, 32%

Ar = 4-$MeOC_6H_4$.

oxopropionate (**I**). Nucleophilic attack on esters **II** and **III** can be directed at both carbonyl groups and activated double C=C bond. The predominant pathway in the reactions with nucleophiles is addition–elimination at the C=C bond with replacement of the ethoxy or arylamino group. These transformations may be accompanied by intramolecular cyclization involving the pentafluorophenyl moiety.

EXPERIMENTAL

The IR spectra (4000–400 cm^{-1}) were recorded on a Perkin–Elmer Spectrum I Fourier spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were measured on a Bruker DRX-400 spectrometer (400 MHz) relative to tetramethylsilane, and the ^{19}F NMR spectra were obtained on a Tesla BS-587A instrument (75 MHz) using C_6F_6 as reference. The elemental composition were determined on a Carlo Erba CHNS-O EA 1108 analyzer. The mass spectrum (electron impact, 70 eV) was run on a Varian MAT-311A mass spectrometer with direct sample admission into the ion source.

Esters **II** and **III** were synthesized by the procedure described in [1]. Ester **IIIc** was not reported previously.

Ethyl 3-(4-methoxyphenylaminomethylidene)-2,4-dioxo-4-pentafluorophenylbutanoate (IIIc) (mixture of *Z* and *E* isomers, 9:11**).** Yield 67%, colorless powder, mp 113–114°C (from methanol). IR spectrum, ν, cm^{-1}: 3195, 1610 (NH); 1744 (CO_2Et); 1640 (C=O); 1625, 1586 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: *Z* isomer: 1.35 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.2 Hz), 3.83 s (3H, OCH_3), 4.26 q (2H, $OC\mathbf{H}_2CH_3$, J = 7.2 Hz), 7.92 d.t (1H, =CH, J_{HH} = 13.9, J_{HF} = 2.2 Hz), 12.48 br.d (1H, NH, J = 13.9 Hz); *E* isomer: 1.37 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.2 Hz), 3.85 s (3H, OCH_3), 4.28 q (2H, $OC\mathbf{H}_2CH_3$, J = 7.2 Hz), 8.76 d (1H, =CH, J_{HH} = 13.9 Hz), 12.88 br.d (1H, NH, J = 13.9 Hz); *Z*/*E*: 6.94–7.27 m (4H, C_6H_4). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: *Z* isomer: 2.35 m (2F), 11.48 m (1F), 22.22 m (2F); *E* isomer: 0.25 m (2F), 8.43 m (1F), 18.85 m (2F). Found, %: C 54.17; H 3.35; F 21.77; N 2.92. $C_{20}H_{14}F_5NO_5$. Calculated, %: C 54.19; H 3.18; F 21.42; N 3.16.

Ethyl 4-pentafluorobenzoyl-1*H*-pyrazole-5-carboxylate (IVa). *a*. To a solution of 733 mg (2 mmol) of ester **II** in 10 ml of glacial acetic acid we added 1 ml of 40% hydrazine hydrate. The mixture was stirred for 14 h at room temperature, poured into water, and extracted with chloroform. The extract was washed with distilled water until neutral reaction (pH ≈ 7), dried over $MgSO_4$, and evaporated, and the residue was recrystallized from diethyl ether. Yield 402 mg (60%), colorless powder, mp 119–120°C. IR spectrum, ν, cm^{-1}: 3143, 1610 (NH); 1732 (CO_2Et); 1714 (COC_6F_5); 1686, 1662 (C=N, C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.1 Hz), 4.31 q (2H, $OC\mathbf{H}_2CH_3$, J = 7.1 Hz), 8.26 s (1H, CH), 13.38 br.s (1H, NH). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 1.14 m (2F), 12.02 m (1F), 21.10 m (2F). Mass spectrum, *m*/*z* (I_{rel}, %): 334 (45.46) M^+, 290 (23.54), 289 (33.07), 262 (9.03), 243 (11.67), 195 (44.51) [C_6F_5CO], 167 (83.41), 139 (100.00), 121 (38.52), 93 (11.02), 67 (7.64), 65 (8.16). Found, %: C 46.83; H 1.87; F 28.52; N 8.63. $C_{13}H_7F_5N_2O_3$. Calculated, %: C 46.72; H 2.11; F 28.42; N 8.38.

b. To a solution of 416 mg (0.97 mmol) of ester **IIIb** in 10 ml of glacial acetic acid we added 0.5 ml of 40% hydrazine hydrate. The mixture was stirred for 48 h at room temperature and diluted with 100 ml of distilled water. The precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 228 mg (56%), mp 119–120°C.

Following the above procedure (method *b*), from 1.239 g (3 mmol) of ester **IIIa** and 1.5 ml of 40% hydrazine hydrate we obtained 67 mg (66%) of compound **IVa** with mp 119–120°C.

Ethyl 4-pentafluorobenzoyl-1-phenyl-1*H*-pyrazole-5-carboxylate (IVb). To a solution of 733 mg (2 mmol) of ester **II** in 10 ml of 2-propanol we added 0.2 ml (2.1 mmol) of phenylhydrazine in 2 ml of 2-propanol. The mixture was stirred for 30 min at room temperature, poured into distilled water, and treated with chloroform. The organic phase was washed with water, dried over $MgSO_4$, and evaporated, and the residue was recrystallized from diethyl ether. Yield 396 mg (46%), colorless powder, mp 127–128°C. IR spectrum, ν, cm^{-1}: 3103 (CH), 1740 (CO_2Et), 1666 (COC_6F_5), 1654 (C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.67 t (3H, $OCH_2C\mathbf{H}_3$), 4.24 q (2H, $OC\mathbf{H}_2CH_3$), 7.50–7.51 m (5H, C_6H_5), 7.92 s (1H, =CH). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 1.95 m (2F), 12.18 m (1F), 21.63 m (2F). Found, %: C 55.84; H 2.61; F 22.92; N 6.56. $C_{19}H_{11}F_5N_2O_3$. Calculated, %: C 55.62; H 2.70; F 23.15; N 6.83.

Following a similar procedure, from 443 mg (1 mmol) of ester **IIIc** and 0.1 ml (1 mmol) of phenylhydrazine we obtained 307 mg (75%) of compound **IVb** with mp 127–128°C.

3-[2-(2-Aminophenylamino)-1-pentafluorobenzoylethenyl]-1,2-dihydroquinoxalin-2-one (Va) (mixture of *Z* and *E* isomers, 7:10)**.** To a solution of 733 mg (2 mmol) of ester **II** in 10 ml of anhydrous ethanol we added a solution of 324 mg (3 mmol) of *o*-phenylenediamine in 2 ml of anhydrous ethanol. The mixture was kept for 3 h at room temperature, and the precipitate was filtered off, washed with ethanol, and dried under reduced pressure. Yield 312 mg (66%), yellow powder, mp 318–319°C. IR spectrum, ν, cm^{-1}: 3445, 3360 (NH_2); 3150, 1560 (NH); 3090 (CH); 1665 (CONH); 1650 (COC_6F_5); 1560, 1550 (C=N, C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: *Z*/*E*: 6.61–7.78 m (8H, C_6H_4), 12.37 br.s (1H, NH); *Z* isomer: 5.19 br.s (2H, NH_2), 8.79 d (1H, CH, J_{HH} = 14.7 Hz), 12.25 d (1H, NH, J_{HH} = 14.7 Hz); *E* isomer: 5.05 br.s (2H, NH_2), 7.98 d (1H, CH, J_{HH} = 14.6 Hz), 10.04 d (1H, NH, J_{HH} = 14.6 Hz). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: *Z* isomer: 0.98 m (2F), 8.13 m (1F), 21.57 m (2F); *E* isomer: 0.15 m (2F), 7.45 m (1F), 19.71 m (2F). Found, %: C 58.27; H 2.59; F 19.99; N 11.81. $C_{23}H_{13}F_5N_4O_2$. Calculated, %: C 58.48; H 2.77; F 20.11; N 11.86.

3-[2-(4-Methoxyphenylamino)-1-pentafluorobenzoylethenyl]-1,2-dihydroquinoxalin-2-one (Vb) (mixture of *Z* and *E* isomers, 9:11)**.** To a solution of 330 mg (0.75 mmol) of ester **IIIc** in 10 ml of methanol we added 17 mg (2.2 mmol) of *o*-phenylenediamine and 0.02 ml of trifluoroacetic acid. The mixture was heated for 2 h under reflux and evaporated, and the residue was recrystallized from methanol. Yield 157 mg (43%), colorless powder, mp >300°C. IR spectrum, ν, cm^{-1}: 3446, 3152, 1562 (NH); 3090 (CH); 1667 (CONH); 1660 (COC_6F_5); 1566 (C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: *Z*/*E*: 6.78–7.97 m (8H, C_6H_4), 12.35 br.s (2H, NH); *Z* isomer: 3.73 s (3H, OCH_3), 10.09 d (1H, CH, *J* = 13.9 Hz); *E* isomer: 3.79 s (3H, OCH_3), 8.78 d (1H, CH, *J* = 13.9 Hz). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: *Z* isomer: 0.75 m (2F), 7.87 m (1F), 20.57 m (2F); *E* isomer: 0.00 m (2F), 7.34 m (1F), 19.28 m (2F). Found, %: C 59.09; H 2.78; F 19.50; N 8.87. $C_{24}H_{14}F_5N_3O_3$. Calculated, %: C 59.15; H 2.90; F 19.49; N 8.62.

3-[1-(2-Aminophenyl)-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl]-1,2-dihydroquinoxalin-2-one (VIa) and 3-[5,6,7,8-tetrafluoro-1-(4-methoxyphenyl)-4-oxo-1,4-dihydroquinolin-3-yl]-1,2-dihydroquinoxalin-2-one (VIb). To a solution of 443 mg (1.0 mmol) of ester **IIIc** in 10 ml of methanol we added a solution of 324 mg (3.0 mmol) of *o*-phenylenediamine in 10 ml of methanol. The mixture was heated for 6 h under reflux and diluted with 50 ml of distilled water, and the precipitate was filtered off and was subjected to column chromatography on silica gel (100–250 μm) using chloroform as eluent to isolate 131 mg (32%) of compound **VIa** and 145 mg (28%) of **VIb**.

Compound **VIa**. Yellow powder, mp 322–324°C. IR spectrum, ν, cm^{-1}: 3444, 3357 (NH_2); 3220 (NH); 1680 (CONH); 1634, 1582 (C=N, C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 6.48 br.s (2H, NH_2), 6.62–7.78 m (8H, C_6H_4), 7.93 s (1H, =CH), 12.44 br.s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –1.52 m (1F), 10.41 m (1F), 11.20 m (1F), 17.85 m (1F). Found, %: C 60.23; H 2.60; F 17.19; N 12.48. $C_{23}H_{12}F_4N_4O_2$. Calculated, %: C 60.01; H 2.75; F 17.26; N 12.72.

Compound **VIb**. Yellow powder, mp 265–266°C. IR spectrum, ν, cm^{-1}: 3215, 1585 (NH); 1680 (CONH); 1640 (C=N, C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.84 s (3H, OCH_3), 7.09–7.78 m (8H, C_6H_4), 8.12 s (1H, =CH), 12.47 br.s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –0.51 m (1F); 10.02 m (1F); 11.23 m (1F); 18.52 m (1F). Found, %: C 61.53; H 2.92; F 15.98; N 8.76. $C_{24}H_{13}F_4N_3O_3$. Calculated, %: C 61.68; H 2.80; F 16.26; N 8.99.

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