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

Synthesis of Fluorine-Containing 2-(1-Aryl-4-oxo-1,4-dihydrocinnolin-3-yl)-2-oxoacetic Acids

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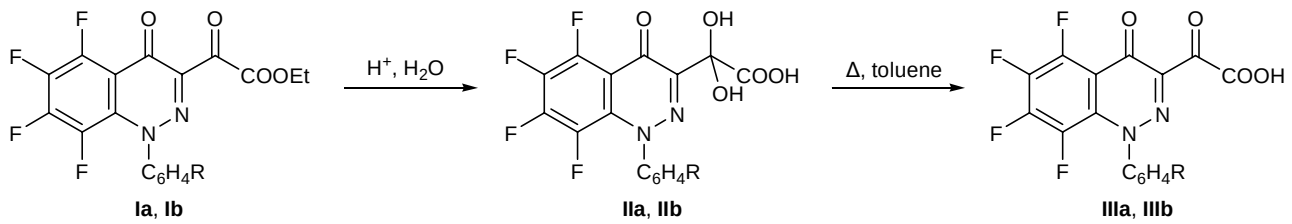
Abstract—Acid hydrolysis of ethyl 2-(1-aryl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydrocinnolin-3-yl)-2-oxoacetates gives 2-(1-aryl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydrocinnolin-3-yl)-2,2-dihydroxyacetic acids which undergo dehydration on heating in toluene to afford 2-(1-aryl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydrocinnolin-3-yl)-2-oxoacetic acids. Reactions of the latter with excess morpholine result in replacement of two fluorine atoms in positions *5* and *7* by the amine residues.

Synthesis of new cinnoline systems attracts a keen interest, for numerous cinnoline derivatives exhibit biological activity [1]. Furthermore, fluorine-containing 4-oxo-1,4-dihydrocinnoline-3-carboxylic acids are aza analogs of known fluoroquinolinone antibiotics which are widely used in medicine [2].

We previously synthesized ethyl 2-(1-aryl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydrocinnolin-3-yl)-2-oxoacetates and their numerous derivatives [3–5]. The goal of the present work was to obtain fluorine-containing 2-(1-aryl-4-oxo-1,4-dihydrocinnolin-3-yl)-2-oxoacetic acids. Acid hydrolysis of ethyl 2-(1-aryl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydrocinnolin-3-yl)-2-oxoacetates **Ia** and **Ib** in a mixture of sulfuric and acetic acids gives the corresponding acids **IIIa** and **IIIb** (Scheme 1). However, unlike 2-[1-alkyl(aryl)-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydrocinnolin-3-yl]-2-oxoacetic acids synthesized previously [6], the isolated hydrolysis products were dihydroxy derivatives **IIa** and **IIb**. The latter are readily converted into oxo acids **IIIa** and **IIIb** by heating in boiling toluene with simultaneous removal of liberated water as azeotrope.

According to the IR and ^{1}H NMR spectra, compounds **IIa** and **IIb** are stable geminal diols formed via addition of water at the α-carbonyl group of the oxalyl fragment. No α-carbonyl absorption band was present in the IR spectra of acids **IIa** and **IIb**, while the corresponding band in the spectra of oxo acids **IIIa** and **IIIb** was observed at about 1700 cm^{-1}. In addition, the acid carbonyl band in the IR spectra of **IIIa** and **IIIb** was displaced by ~20 cm^{-1} to lower frequencies, as compared to dihydroxy compounds **IIa** and **IIb**: 1720–1725 and 1740–1745 cm^{-1}, respectively. This low-frequency shift results from conjugation between the carboxy and α-carbonyl groups in **IIIa** and **IIIb**. The ^{1}H NMR spectra of compounds **IIa** and **IIb** contained a broadened two-proton singlet at δ ~4–5 ppm due to hydroxy protons.

Scheme 1.



Ia, **Ib** **IIa**, **IIb** **IIIa**, **IIIb**

R = H (**a**), 4-MeO (**b**).

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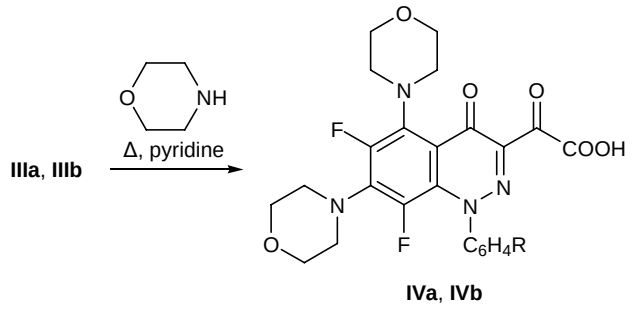
We also demonstrated that fluorine atoms in 2-(1-aryl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydrocinnolin-3-yl)-2-oxoacetic acids **IIIa** and **IIIb** can be replaced by amino groups via reaction with dialkylamines using morpholine as an example. According to published data on transformations of structurally related compounds, their reactions with alkylamines usually give products of fluorine replacement in position *5* or *7* of the heteroring while the fluorine atom in position *8* is replaced in a few specific cases [7, 8]. The formation of 5,7-diamino derivatives occurs fairly rarely. As a rule, the 6-fluorine atom is inactive in these reactions [8].

We recently found conditions ensuring selective replacement of fluorine atoms in ethyl 2-(1-aryl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydrocinnolin-3-yl)-2-oxoacetates and their 3-hetaryl-substituted analogs in reactions with morpholine [5]. When these reactions were performed in DMSO at room temperature, 7-monosubstituted products were mainly formed, while heating in boiling pyridine favored formation of 5,7-disubstituted derivatives.

By reacting acids **IIIa** and **IIIb** with excess morpholine in boiling pyridine we obtained the corresponding 5,7-dimorpholino derivatives **IVa** and **IVb** (Scheme 2). However, we failed to obtain 7-monosubstituted compounds, presumably due to insignificant difference in the reactivity of fluorine atoms in positions *5* and *7*.

Scheme 2.



R = H (**a**), 4-MeO (**b**).

The site of substitution was established on the basis of coupling constants in the ^{19}F NMR spectra with account taken of published data. In the spectra of acids **IVa** and **IVb**, the coupling constant between fluorine atoms in positions *6* and *8* ($J_{6,8} = J_{8,6} = 6$ Hz) was typical of *meta* interaction in polyfluorinated aromatic systems [9].

EXPERIMENTAL

The IR spectra were recorded on a Perkin–Elmer Spectrum One Fourier spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were obtained on a Bruker DRX-400 instrument (400 MHz) using tetramethylsilane as reference. The ^{19}F NMR spectra were measured on Tesla BS-587A (75.3 MHz) and Bruker DRX-400 instruments; the chemical shifts were measured relative to C_6F_6. The elemental compositions were determined on a Carlo Erba CHNS-O EA 1108 analyzer.

Ethyl 2-(1-aryl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydrocinnolin-3-yl)-2-oxoacetates **Ia** and **Ib** were synthesized by the procedure described in [3].

2,2-Dihydroxy-2-(5,6,7,8-tetrafluoro-4-oxo-1-phenyl-1,4-dihydrocinnolin-3-yl)acetic acid (IIa). A mixture of 2.7 ml of water, 3.5 ml of glacial acetic acid, and 0.5 ml of concentrated sulfuric acid was added to 597 mg (1.5 mmol) of ester **Ia**, the mixture was heated for 30 min, 10 ml of water was added, the mixture was cooled to 5°C, and the precipitate was filtered off and washed with cold distilled water. Yield 446 mg (81%), yellow powder, mp 232–233°C. IR spectrum, ν, cm^{-1}: 3285, 3090 (OH); 1740 (CO_2H); 1640 (C=O); 1590 (C=C). ^1H NMR spectrum [$(CD_3)_2CO$], δ, ppm: 4.67 br.s (2H, OH); 7.52–7.73 m ($5H_{arom}$), 11.5 br.s (1H, COOH). ^{19}F NMR spectrum [$(CD_3)_2CO$], δ_F, ppm: 4.63 m (1F); 17.08 m (1F); 21.26 m (1F); 22.26 m (1F). Found, %: C 49.94; H 1.93; F 19.86; N 7.18. $C_{16}H_8F_4N_2O_5$. Calculated, %: C 50.01; H 2.10; F 19.78; N 7.29.

2,2-Dihydroxy-2-[5,6,7,8-tetrafluoro-1-(4-methoxyphenyl)-4-oxo-1,4-dihydrocinnolin-3-yl]acetic acid (IIb) was synthesized in a similar way from 1.045 g (2.5 mmol) of ester **Ib**. Yield 654 mg (88%), yellow powder, mp 122–123°C. IR spectrum, ν, cm^{-1}: 3310, 3080 (OH); 1745 (COOH); 1640 (C=O); 1590 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.89 s (3H, OCH_3), 4.36 br.s (2H, OH), 7.19 m (4H, C_6H_4), 11.7 br.s (1H, COOH). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 6.98 m (1F), 19.58 m (1F), 21.76 m (1F), 23.75 m (1F). Found, %: C 49.20; H 2.53; F 18.25; N 6.56. $C_{17}H_{10}F_4N_2O_6$. Calculated, %: C 49.29; H 2.43; F 18.34; N 6.76.

2-Oxo-2-(5,6,7,8-tetrafluoro-4-oxo-1-phenyl-1,4-dihydrocinnolin-3-yl)acetic acid (IIIa). A solution of 1.152 g (3.0 mmol) of compound **IIa** in 30 ml of toluene was heated for 3 h under reflux with simultaneous removal of liberated water. The solvent was

distilled off under reduced pressure to isolate 1.043 g (95%) of acid **IIIa** as a yellow powder with mp 145–146°C. IR spectrum, ν, cm^{-1}: 3070 (OH), 1720 (COOH), 1705 (α-C=O), 1640 (C=O), 1590 (C=C). ^1H NMR spectrum [$(CD_3)_2CO$], δ, ppm: 7.44–7.65 m (5H, H_{arom}), 12.5 br.s (1H, COOH). ^{19}F NMR spectrum [$(CD_3)_2CO$], δ_F, ppm: 4.73 m (1F), 17.12 m (1F), 20.23 m (1F), 21.03 m (1F). Found, %: C 52.44; H 1.73; F 20.86; N 7.58. $C_{16}H_6F_4N_2O_4$. Calculated, %: C 52.47; H 1.65; F 20.75; N 7.65.

2-Oxo-2-[5,6,7,8-tetrafluoro-1-(4-methoxyphenyl)-4-oxo-1,4-dihydrocinnolin-3-yl]acetic acid (IIIb) was synthesized in a similar way from 1.296 g (3.1 mmol) of compound **IIb**. Yield 1.220 g (95%), yellow powder, mp 118–119°C. IR spectrum, ν, cm^{-1}: 3085 (OH); 1725 (COOH); 1700 (α-C=O); 1640 (C=O); 1590 (C=C). ^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm: 3.86 s (3H, OCH_3); 7.35 m (4H_{arom}), 11.8 br.s (1H, COOH). ^{19}F NMR spectrum [$(CD_3)_2SO$], δ_F, ppm: 4.73 m (1F), 16.79 m (1F), 19.50 m (1F), 20.63 m (1F). Found, %: C 51.77; H 2.11; F 18.73; N 7.03. $C_{17}H_8F_4N_2O_5$. Calculated, %: C 51.53; H 2.04; F 19.18; N 7.07.

2-(6,8-Difluoro-5,7-dimorpholino-4-oxo-1-phenyl-1,4-dihydrocinnolin-3-yl)-2-oxoacetic acid (IVa). Morpholine, 58 mg (4 mmol), was added to a solution of 366 mg (1 mmol) of acid **IIIa** in 10 ml of anhydrous pyridine, the mixture was heated for 30 min and evaporated, and the residue was dissolved in a mixture of 20 ml of chloroform and 20 ml of water. The organic phase was separated, washed with water, dried over $MgSO_4$, and evaporated, and the residue was recrystallized from diethyl ether. Yield 400 mg (80%), yellow powder, mp 167–168°C. IR spectrum, ν, cm^{-1}: 2720 (OH), 1725 (COOH), 1705 (α-C=O), 1645 (C=O), 1595 (C=C). ^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm: 3.29–3.78 m (16H, CH_2); 7.15–7.35 m (5H, H_{arom}); 10.75 (1H, OH). ^{19}F NMR spectrum [$(CD_3)_2SO$], δ_F, ppm: 27.11 d (1F, J = 6.0 Hz); 33.51 d (1F, J = 6.0 Hz). Found, %: C 57.45; H 4.59; F 7.71; N 11.12. $C_{24}H_{22}F_2N_4O_6$. Calculated, %: C 57.60; H 4.40; F 7.59; N 11.20.

2-[6,8-Difluoro-1-(4-methoxyphenyl)-5,7-dimorpholino-4-oxo-1,4-dihydrocinnolin-3-yl]-2-oxoacetic acid (IVb) was synthesized in a similar way from 277 mg (0.7 mmol) of acid **IIIb** and 51 mg (3.5 mmol) of morpholine. Yield 301 mg (81%), yellow powder, mp 154–155°C. IR spectrum, ν, cm^{-1}: 2714 (OH), 1721 (COOH), 1700 (α-C=O), 1640 (C=O), 1589 (C=C). ^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm: 3.27–3.93 m (16H, CH_2), 3.88 s (3H, OCH_3), 7.17 m (4H, H_{arom}), 10.11 (1H, OH). ^{19}F NMR spectrum [$(CD_3)_2SO$], δ_F, ppm: 29.36 d (1F, J = 6.0 Hz) 31.29 d (1F, J = 6.0 Hz). Found, %: C 56.52; H 4.68; F 7.45; N 10.47. $C_{25}H_{24}F_2N_4O_7$. Calculated, %: C 56.60; H 4.56; F 7.16; N 10.56.

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