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Synthesis of Derivatives of Pyrazolo[1,5-*a*]pyrimidines and Imidazo[1,5-*a*]pyrimidines proceeding from Alkyl 2-Benzylidene-3-oxo-3-fluoroalkylpropionates

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Abstract—Methods were developed of the synthesis of alkyl 2-hydroxy-2-fluoroalkyl-4-phenyl-1,2,3,4—tetrahydroimidazo-[1,5-*a*]pyrimidine-3-carboxylates and alkyl-5-hydroxy-2,7-diphenyl-5-fluoroalkyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-6-carboxylates by regioselective [3+3]-cycloaddition of 5-aminoimidazole or 5-aminopyrazole to alkyl 2-benzylidene-3-oxo-3-fluoroalkylpropionates at the fluoroacylvinyl fragment.

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Azoloazines constitute an important class of biologically active compounds for they include a group of purine bases playing a significant role in the vital activity of organisms [1]. A special interest attract azolopyrimidines, structural analogs (isosters) of purine bases, some families of which are endowed with antiviral action [2]. We showed recently that 2-arylmethylene-3-oxo-3-fluoroalkylpropionates are convenient blocks for preparation of 7-aryl-6-alkoxycarbonyl-5-fluoroalkyl-1,2,4-triazolo-[1,5-*a*]-pyrimidines and 7-aryl-6-alkoxycarbonyl-5-fluoroalkyltetrazolo[1,5-*a*]pyrimidines by reactions with 3-amino-1,2,4-triazole and 5-aminotetrazole [3].

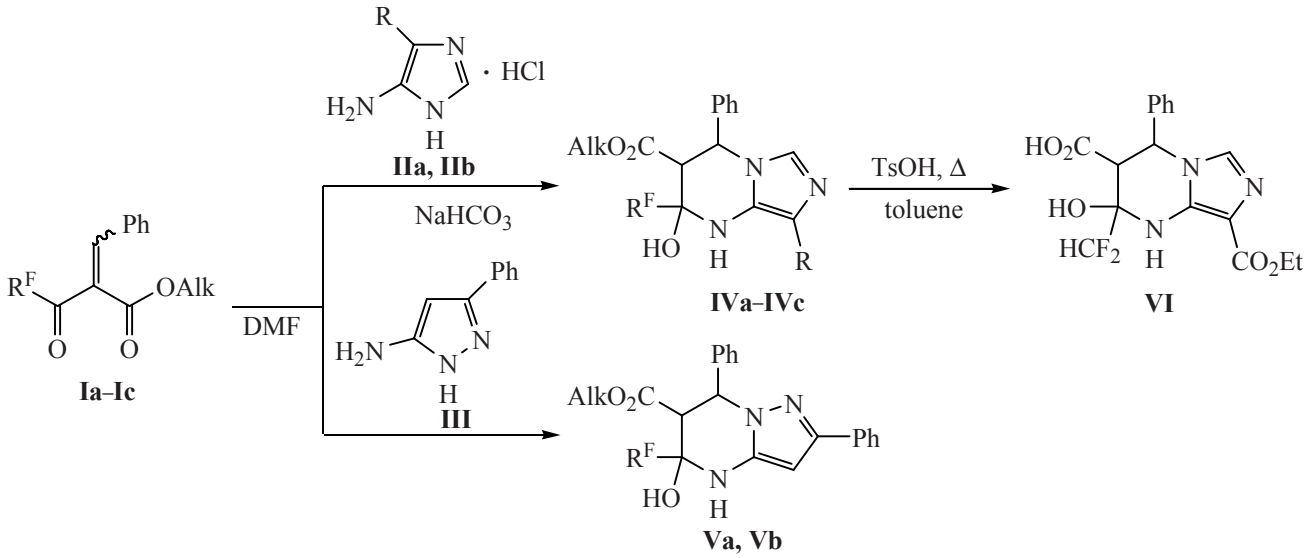
In this study we investigated the ways of building up derivatives of pyrazolo[1,5-*a*]pyrimidine and imidazo-[1,5-*a*]pyrimidine by reactions of alkyl 2-benzylidene-3-oxo-3-fluoroalkylpropionates **Ia–Ic** with 5-aminoimidazoles **IIa** and **IIb** and 5-amino-pyrazole (**III**).

Initial esters **Ia–Ic** contain three nonequivalent electrophilic reaction sites that might be attacked by a nucleophile: the alkoxycarbonyl carbon atom, the carbonyl atom of the polyfluoroacyl group, and the carbon atom of the methylidene fragment. The dinucleophilic reagents used in the study **IIa, IIb**, and **III** also contain two unequal reaction sites and can react with the substrates in various combinations. In this connections the reactions of esters **Ia–Ic** with diamines **IIa, IIb**, and **III** can provide isomers of various structures.

It was found that esters **Ia–Ic** reacted both with 5-aminoimidazoles **IIa** and **IIb** and with 5-amino-3-phenylpyrazole (**III**) regioselectively at the polyfluoroacylvinyl fragment giving the corresponding alkoxycarbonyl-substituted tetrahydroimidazopyrimidines **IVa–IVc** and tetrahydropyrazolopyrimidines **Va** and **Vb** (Scheme 1). The reactions were carried out by heating in DMF. The use of other organic solvents (ethanol, benzene) was inefficient for either tarring occurred or the conversion of initial substrates **Ia–Ic** was incomplete.

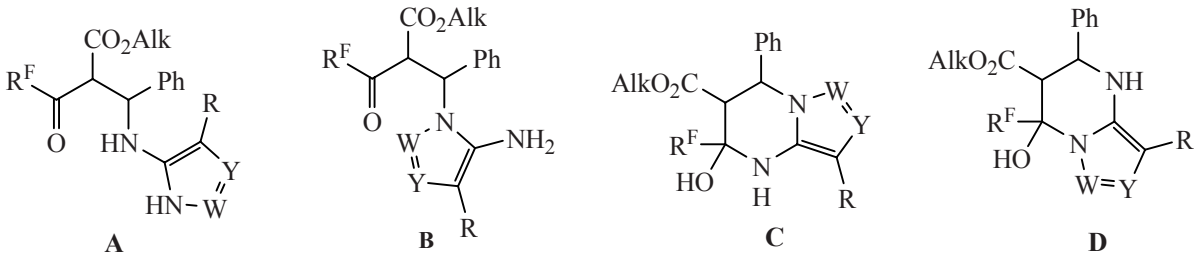
The cyclic nature of compounds **IVa–IVc, Va, Vb** and not the isomeric structure with an open chain [isomers **A**, **B** (Scheme 2)] was confirmed by their spectral characteristics. For instance, in the IR spectra of monoalkoxycarbonyl-containing compounds **IVc, Va**, and **Vb** recorded in mineral oil appeared a single high-frequency band (ν 1743–1706 cm^{-1}), and in each spectrum of dialkoxycarbonyl-substituted products **IVa** and **IVb** two bands were observed (ν 1752–1654 cm^{-1}) corresponding to the stretching vibrations of the ester carbonyl group as was characteristic of cyclic forms **C** and **D**. The

Scheme 1.



I, $R^F = HCF_2$, Alk = Me (**a**); $R^F = CF_3$, Alk = Et (**b**); $R^F = H(CF_2)_2$, Alk = Me (**c**); **II**, R = CO_2Et (**a**), NO_2 (**b**); **IV**, $R^F = HCF_2$, Alk = Me, R = CO_2Et (**a**); $R^F = CF_3$, Alk = Et, R = CO_2Et (**b**), NO_2 (**c**); **V**, $R^F = CF_3$, Alk = Et (**a**); $R^F = H(CF_2)_2$, Alk = Me (**b**).

Scheme 2.



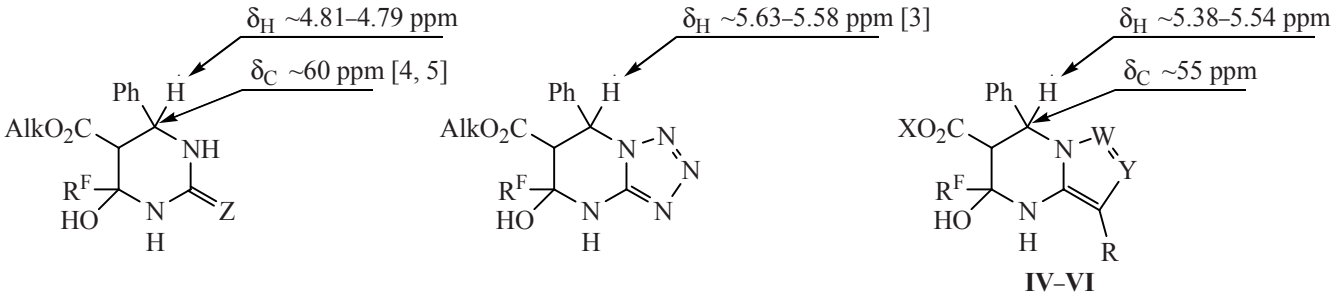
W = CH, Y = N (**IV**), W = N, Y = CHPh (**V**).

signals of fluorine atoms of the groups α-CF_3- and α-CF_2 in the ^{19}F NMR spectra of compounds **IVa–IVc, Va, Vb** taken in $(CD_3)_2SO$ were observed in a strong field [δ(CF_3) ~81–82, δ(CF_2) ~31–35 ppm) indicating that these groups were contiguous to the quaternary carbon atom of the cyclic isomers **C** and **D** (Scheme 2) [3].

The data of ^1H, ^{19}F NMR and IR spectra cannot be decisive for the choice between the possible structures **C** and **D** of heterocycles **IVa–IVc, Va, Vb**. For compound **IVb** additional measurements were performed of spectra 2D ^1H–^{13}C HSQC and 2D ^1H–^{13}C HMBC (see the table). It turned out that the spectrum 2D ^1H–^{13}C HMBC contained cross-peaks of groups HO and NH with atom C^3 which was possible for both isomers **C** and **D**. However in this spectrum was absent a cross-peak between the proton of NH group and atom C^4 that should be present in the case of isomer **D**. The registering of the spectrum 2D ^1H–^{13}C HSQC made it possible more precise assignment of the protonated carbon atoms.

The comparison of ^1H, ^{13}C NMR spectral characteristics of compounds **IVa–IVc, Va, Vb**, **VI** with the data of previously obtained alkyl 5-hydroxy-7-phenyl-5-fluoroalkyl-4,5,6,7-tetrahydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylates [3] having a structure analogous to that of isomer **C**, and of alkyl 2-oxo(thioxo)-6-phenyl-4-fluoroalkylhexahydropyrimidine-5-carboxylates [4, 5] containing a structural fragment Ph–CH–NH present in isomer **D** permits the assignment to tetrahydroazolopyrimidines **IVa–IVc, Va, Vb**, **VI** the structure of isomer **C**.

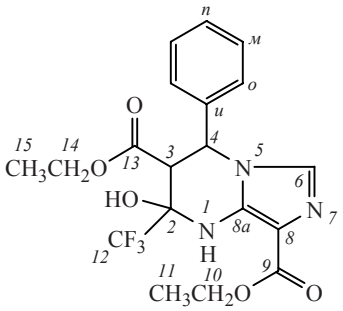
We failed to obtain heterocycles **IVa–IVc, Va, Vb** by three-component condensation of esters **I** with aldehydes and aminoazoles **IIa, IIb** and **III** unlike analogous reactions with 3-amino-1,2,4-triazole and 5-aminotetrazole [3]. Besides in reactions of esters **I** with the latter



IV–VI

aminoazoles the main products were dihydrotri(tetr)azolo-[1,5-*a*]pyrimidines, and only in reactions with 5-aminotetrazole were isolated tetrahydrotetrazolo[1,5-*a*]-pyrimidines containing the hydroxy group at the cyclic carbon atom bearing the fluoroalkyl substituent. Therewith the tetrahydrotetrazolo[1,5-*a*]-pyrimidines at boiling in toluene in the presence of *p*-toluenesulfonic acid readily underwent dehydration into the corresponding dihydrotetrazolo[1,5-*a*]pyrimidines [3].

^{13}C NMR spectrum of compound **IVb** in $(CD_3)_2SO$



Atom	δ, ppm (J_{C-F}, Hz)
C^2	80.05 br.q (*J* 30.9)
C^3	49.65
C^4	55.19
C^6	129.82
C^8	140.40
C^{8a}	110.37
C^9	163.37
C^{10}	59.09
C^{11}	13.40
C^{12}	123.11 q (*J* 286.1)
C^{13}	165.94
C^{14}	60.84
C^{15}	14.37
C^{θ}	134.53
C^{O}	128.91
C^{m}	129.00
C^{n}	129.55

The attempts to carry out the dehydration of heterocycles **IVa–IVc, Va, Vb** under similar conditions or by heating in acetic acid always resulted in formation of intractable mixtures. Only from compound **IVa** we succeeded to obtain a small amount of tetrahydroimidazopyrimidinecarboxylic acid **VI** formed by hydrolysis of one of the ester groups (Scheme 1).

The XRD analysis of a single crystal of acid **VI** showed that this compound has a structure of 2-hydroxy-2-difluoromethyl-4-phenyl-8-ethoxycarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]-pyrimidine-3-carboxylic acid (see the figure). This information confirmes our isomer assignment of heterocycles **IVa–IVc, Va, Vb , VI**.

Besides the ^{1}H NMR and XRD data show, that the hydrolysis in compound **IVa** occurred at the methoxycarbonyl group of the tetrahydropyrimidine part of the molecule whereas the ester substituent in the imidazole fragment remained intact. The higher resistance to the hydrolysis of this substituent may be due to its conjugation with the imidazole ring or by involvement into an intramolecular hydrogen bond with the NH group of the tetrahydropyrimidine ring. The presence of an intramolecular hydrogen bond is suggested by the data of IR spectra of compounds **IVa** and **IVb** having an ethoxycarbonyl substituent at the imidazole ring which contains low-frequency absorption bands (ν 1660–1654 cm^{-1}) of the stretching vibrations of the ester carbonyl group.

Analogous intramolecular hydrogen bond is also present in acid **VI** as confirmed by the XRD data: intramolecular distance $O^1\cdots H^1$ is 2.39(6) Å, angles N^1–$H^1\cdots O^1$ and C^9–$O^1\cdots H^1$ equal 121.89 and 99.63°.

In the molecule of acid **VI** a formation is possible of one more intramolecular hydrogen bond between the OH group and the carboxy moiety of the tetrahydropyrimidine ring, but the XRD data exclude this possibility.

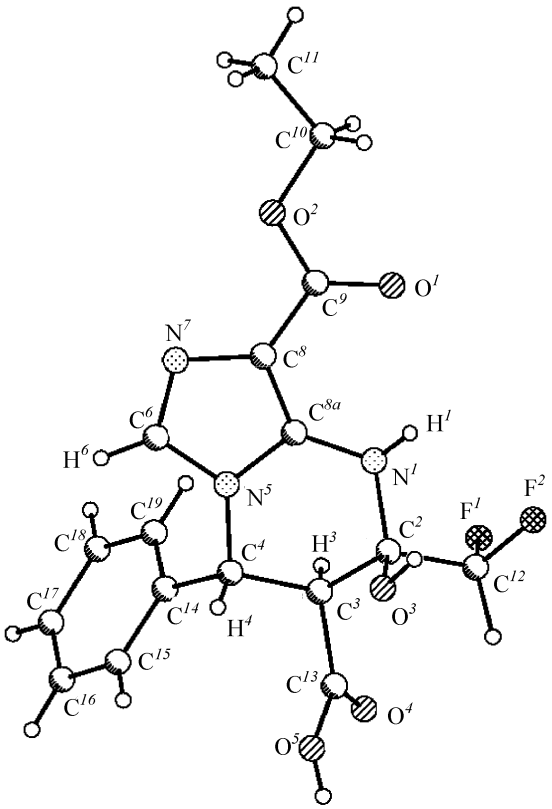
Tetrahydroimidazo- and -pyrazolo[1,5-*a*]pyrimidines **IVa–IVc, Va, Vb , VI** contain three asymmetric carbon atoms and therefore four diastereomeric forms are

presumable for them. However their NMR spectra indicate the presence in each case of a single form. The coupling constant [$J(H^3–H^4)$ 10.9–12.0 Hz] for protons at the phenyl and alkoxycarbonyl substituents in the ^{1}H NMR spectra of compounds **IVa–IVc, Va, Vb , VI** corresponds to their axial-axial coupling [6]. The values of conformational energies for the groups CF_3 [$\Delta G(CF_3)$ 8.8 kJ mol^{-1}] and OH [ΔG(OH) 2.28 kJ mol^{-1}] reported in [7] for substituted cyclohexanones make it possible to suggest the preferable equatorial position of the polyfluoroalkyl substituent. In keeping with the above reasoning in compounds **IVa–IVc, Va, Vb , VI** apparently exists the conformation with the equatorial orientation of the phenyl, alkoxycarbonyl, and fluoroalkyl groups. This is confirmed by the XRD data on acid **VI** that show the equatorial position of the bulky substituents (phenyl, difluormethyl, and carboxy groups) and axial orientation of atoms H^3, H^4 , and OH group (see the figure).

In case of compounds **IVa** and **IVb** containing an ethoxycarbonyl substituent in the imidazole ring the signal of proton H^3 appeared as a doublet of doublets due to the coupling through three bonds with the proton H^4 (J 11.7–12.0 Hz) and through four bonds with the proton of HO group (J 0.9–1.1 Hz) indicating the *W*-like position of H^3 and HO [8].

In the ^{1}H NMR spectrum of acid **VI** the signal of proton H^3 also possesses a doublet character (J 3.3 Hz), but from a coupling through four bonds with the proton of COOH group, also indicating their *W*-like position. Just this position of these atoms in the molecule of acid **VI** was shown by XRD data (see the figure). Evidently this orientation prevents the formation of an intramolecular bond between the OH group and the carboxy residue of the tetrahydropyrimidine ring.

Thus we demonstrated that esters **I** enter into reactions of regioselective [3+3]-cycloaddition with 5-aminoimidazoles **II** and 5-aminopyrazole (**III**) furnishing [1,5-*a*]-azolofused tetrahydropyrimidines resulting from the addition of the free amino group of azoles to the fluoroacyl fragment of esters **I**, and of α-NH group of the azole to the C=C bond. However the cyclization of esters **I** with hetarylamines is not always regioselective. For instance, from the reaction with 2-aminopyridine we isolated condensation product at the ester fragment, 4-aryl-2-hydroxy-3-polyfluoroacyl-4*H*-pyrido[1,2-*a*]pyrimidines [9]. The reactions of alkyl 2-arylmethylene-3-oxobutanoates with aminoazoles have the same regiodirection, but the addition of the NH_2 group of dinucleophile to the acetyl fragments accompanied with an immediate elimination



Crystal structure of 2-hydroxy-2-difluoromethyl-4-phenyl-8-ethoxycarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]-pyrimidine-3-carboxylic acid (**VI**).

of a water molecule leading to the formation of azolo-[1,5-*a*]pyrimidines [10]. The formation of stable heterocycles including a *gem*-aminoalcohol fragment at the fluoroalkyl substituent is the distinguishing feature of 3-oxo-3-fluoroalkylpropionates compared with the analogs from the hydrocarbon series. This feature originates from the electron-acceptor effect of the fluoroalkyl substituent preventing the easy elimination of the water molecule.

EXPERIMENTAL

Melting points of compounds **IVa–IVc, Va, Vb , VI** were measured on a device Stuart SMP3. IR spectra were recorded on an IR Fourier spectrophotometer Perkin Elmer Spectrum One from mulls in mineral oil. NMR spectra were registered on a spectrometer Bruker DRX-400 (^{1}H: 400 MHz, relative to TMS; ^{19}F: 376 MHz, relative to C_6F_6; ^{13}C: 100 MHz, relative toTMS) in $(CD_3)_2SO$. Elemental analysis was carried out on an analyzer Perkin Elmer 2400 series 2 CHNS-O EA 1108.4. The reaction progress was monitored by TLC on Sorbfil PTSKh-AF-V-UV plates.

X-ray diffraction study of compound VI. The single crystals were grown by slow evaporation of ethanol solution. Crystals monoclinic, M 381.34, $C_{17}H_{17}F_2N_3O_5$, space group $P2_1/c$, a 13.0061(19), b 11.0239(17), c 14.046(3) Å, α 90, β 113.989(15), γ 90 deg, V 1840.0(5) Å^3, Z 4, d_{calc} 1.377 g cm^{-3}, μ(MoK_α) 0.115 cm^{-1}, $(2\theta)_{max}$ 63.32°, λ 0.71073 Å, $F(000)$ 792, $-19 \le h \le 19$, $-15 \le k \le 15$, $-20 \le l \le 20$. The overall number of reflections (29584) was measured on a diffractometer XCalibur 3 at 295(2) K (ш/2θ-scanning, MoK_α radiation, graphite monochromator, CCD-detector), number of independent reflections 5787 (R_{int} 0.0671), number of reflections with $F_o > 4\sigma(F_o)$ 1823. The structure was solved by the direct method and refined by the least-squares method using software SHELXL-97 [11] till R 0.0550, wR_2 0.1026, GOF 1.000. The complete set of crystallographic data is deposited into the Cambridge Structural Database (registered number 662765) and is available at the address www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Initial esters **I** were prepared by procedure [12].

8-methyl, 3-ethyl 2-hydroxy-2-difluoromethyl-4-phenyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidine-3,8-dicarboxylate (IVa). A mixture of 2.40 g (0.01 mol) of ester **Ia**, 1.92 g (0.01 mol) of 5-aminoimidazole hydrochloride (**IIa**), and 1.00 g (0.012 mol) of $NaHCO_3$ in 10 ml of dry DMF was stirred for 8–12 h at 70°C, then cooled and poured into water with ice (~100 ml), the separated precipitate was filtered off, washed with warm water and Et_2O. Yield 2.77 g (70%), colorless powder, mp 187–188°C. IR spectrum, ν, cm^{-1}: 3359, 3110 (O–H, N–H^{stretch}), 1709, 1654 (C=O), 1605, 1524, 1498 (C=C, C=N, N–H^{bend}), 1056–1182 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.26 t (3H, OCH_2CH_3, $^3J_{H-H}$ 7.1 Hz), 1.99 s (3H, OCH_3), 3.56 d.d [1H, H^3, ^3J(H^3–H^4) 12.0, ^4J(H^3–OH) 0.9 Hz], 4.20 q (2H, OCH_2CH_3, $^3J_{H-H}$ 7.1 Hz), 5.53 d [1H, H^4, ^3J(H^4–H^3) 12.0 Hz], 6.33 t (1H, HCF_2, $^2J_{H-F}$ 54.6 Hz), 6.49 s (1H, H^6), 6.92 s (1H, H^1), 7.25 d [1H, OH, J(OH–H^3) 0.9 Hz], 7.42–7.47 m (5H, Ph). ^{19}F NMR spectrum, δ, ppm: 31.12 m (2F, HCF_2, AB system, Δ_{AB} 0.35, $J_{F(A)-F(B)}$ 279.0, J_{F-H} 54.6 Hz). Found, %: C 55.00; H 4.85; F 9.38; N 10.69. $C_{18}H_{19}F_2N_3O_5$. Calculated, %: C 54.69; H 4.84; F 9.60; N 10.63.

Diethyl 2-hydroxy-2-trifluoromethyl-4-phenyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]-pyrimidine-3,8-dicarboxylate (IVb) was obtained similarly from 2.72 g (0.01 mol) of ester **Ib**. Yield 2.78 g (65%), colorless powder, mp 115–116°C. IR spectrum, ν, cm^{-1}: 3353, 3119 (O–H, N–H^{stretch}), 1752, 1661 (C=O), 1614, 1525, 1496 (C=C, C=N, N–H^{bend}), 1204–1093 (C–F). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, OCH_2CH_3, $^3J_{H-H}$ 7.0 Hz), 1.27 t (3H, OCH_2CH_3, $^3J_{H-H}$ 7.1 Hz), 3.58 d.d [1H, H^3, ^3J(H^3–H^4) 11.7, ^4J(H^3–OH) 1.1 Hz], 3.88 m (2H, OCH_2CH_3, AB system, Δ_{AB} 0.01, $^2J_{H(A)-H(B)}$ 10.9, $^3J_{H-H}$ 7.1 Hz), 4.22 q (2H, OCH_2CH_3, $^3J_{H-H}$ 7.0 Hz), 5.49 d [1H, H^4, ^3J(H^4–H^3) 11.7 Hz], 6.58 s (1H, H^6), 6.68 C (1H, H^1), 7.43–7.53 m (5H, Ph), 8.00 d [1H, OH, ^4J(OH–H^3) 1.1 Hz]. ^{19}F NMR spectrum, δ, ppm: 81.4 s (CF_3). Found, %: C 52.92; H 4.58; F 13.33; N 9.93. $C_{19}H_{20}F_3N_3O_5$. Calculated, %: C 53.40; H 4.72; F 13.33; N 9.83.

Ethyl 2-hydroxy-8-nitro-2-trifluoromethyl-4-phenyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidine-3-carboxylate (IVc) was obtained similarly from 2.72 g (0.01 mol) of ester **Ib** and 1.37 g (0.01 mol) of aminoimidazole hydrochloride **IIb**. Yield 2.48 g (62%), colorless powder, mp 178–180°C. IR spectrum, ν, cm^{-1}: 3363, 2963 (N–H^{stretch}, O–H), 1743 (C=O), 1632, 1610, 1535 (C=C, C=N, N–H^{bend}), 1488 (NO_2), 1212–1078 (C–F). ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, OCH_2CH_3, $^3J_{H-H}$ 7.2 Hz), 3.74 d [1H, H^3, ^3J(H^3–H^4) 11.8 Hz], 3.88 m (2H, OCH_2CH_3, AB system, Δ_{AB} 0.02, $^2J_{H(A)-H(B)}$ 10.9, $^3J_{H-H}$ 7.1 Hz), 5.55 d [1H, H^4, ^3J(H^4–H^3) 11.8 Hz], 6.74 s (1H, H^6), 7.44–7.46 m (3H, Ph), 7.58–7.60 m (2H, Ph), 7.63 br.s (1H, OH), 8.28 s (1H, H^1). ^{19}F, δ, ppm: 81.88 s (CF_3). Found, %: C 47.92; H 3.72; F 13.87; N 14.17. $C_{16}H_{15}F_3N_4O_5$. Calculated, %: C 48.01; H 3.78; F 14.00; N 14.24.

Ethyl 5-hydroxy-5-trifluoromethyl-2,7-diphenyl-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-6-carboxylate (Va). A mixture of 2.72 g (0.01 mol) of 3-oxoester **Ib** and 1.91 g (0.01 mol) of 5-amino-3-phenylpyrazole (**III**) in 10 ml of anhydrous DMF was stirred for 5–6 h at 70°C, then cooled and poured into water with ice (~100 ml), the separated precipitate was filtered off and recrystallized from EtOH. Yield 3.02 g (70%), colorless powder, mp 204–206°C. IR spectrum, ν, cm^{-1}: 3399, 3304, 2928 (N–H^{stretch}, O–H), 1715 (C=O), 1593, 1580, 1525, 1513 (C=C, C=N, N–H^{bend}), 1200–1092 (C–F). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, OCH_2CH_3, $^3J_{H-H}$ 7.1 Hz), 3.33 d [1H, H^6, ^3J(H^6–H^7) 11.6 Hz], 3.88 m (2H, OCH_2CH_3, AB system, Δ_{AB} 0.03, $J_{H(A)-H(B)}$ 10.7, $^3J_{H-H}$ 7.1 Hz), 5.46 d [1H, H^7, ^3J(H^7–H^6) 11.6 Hz], 5.88 s (1H, H^3), 7.22–7.54 m (10H, 2Ph), 7.56 s (1H, OH), 7.86 s (1H, H^4). ^{19}F NMR spectrum, δ, ppm: 82.12 s (CF_3). Found, %: C 60.96; H 4.53; F 13.18; N 9.69. $C_{22}H_{20}F_3N_3O_3$. Calculated, %: C 61.25; H 4.67; F 13.21; N 9.74.

Methyl 5-hydroxy-5-(1,1,2,2-tetrafluoroethyl)-2,7-diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylate (Vb) was similarly obtained from 2.90 g (0.01 mol) of 3-oxoester **Ic**. Yield 2.61 g (58%), colorless crystals, mp 197–199°C. IR spectrum, ν, cm^{-1}: 3368, 3292 (N–H^{stretch}, O–H), 1706 (C=O), 1591, 1579, 1525, 1513 (C=C, C=N, N–H^{bend}), 1114–1082 (C–F). ^{1}H NMR spectrum, δ, ppm: 3.38 s (3H, OCH_3), 3.41 d [1H, H^6, ^3J(H^6–H^7) 11.5 Hz], 5.47 d [1H, H^7, ^3J(H^7–H^6) 11.5 Hz], 5.91 s (1H, H^3), 6.71 t.t [1H, H$(CF_2)_2$, $^2J_{H–F}$ 51.2, $^3J_{H–F}$ 6.3 Hz], 7.21–7.40 m (8H, 2 Ph), 7.36 s (1H, OH), 7.52–7.54 m (2H, Ph), 7.53 C (1H, H^4). ^{19}F NMR spectrum, δ, ppm: 27.89 m (2F, HCF_2, *AB* system, Δ_{AB} 0.95, $J_{F(A)–F(B)}$ 295.0, $^2J_{F–H}$ 51.2, $^3J_{F–H}$ 6.3, $^3J_{F–F}$ 9.6 Hz), 35.14 m (2F, CF_2, *AB* system, Δ_{AB} 3.20, $J_{F(A)–F(B)}$ 268.0 Hz). Found, %: C 58.64; H 4.08; F 16.66; N 9.21. $C_{22}H_{19}F_4N_3O_3$. Calculated, %: C 58.80; H 4.26; F 16.91; N 9.35.

2-Hydroxy-2-difluoromethyl-4-phenyl-8-ethoxycarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidine-3-carboxylic acid (VI). A solution of 1.19 g (0.003 mol) of compound **IVa** in 100 ml of toluene in the presence of *p*-toluenesulfonic acid was boiled for 5 days with azeotropic removal of water. Then the hot reaction mixture was filtered, concentrated in a vacuum, and the formed precipitate was recrystallized from EtOH. Yield 0.11 g (10%), colorless crystals, mp 180–182°C. ^{1}H NMR spectrum, δ, ppm: 1.09 t (3H, OCH_2CH_3, $^3J_{H–H}$ 7.0 Hz), 3.89 d.d [H, H^3, ^3J(H^3–H^4) 10.9, J(H^3–CO_2H) 3.3 Hz], 4.21 q (2H, OCH_2CH_3, $^3J_{H–H}$ 7.0 Hz), 5.38 d [1H, H^4, ^3J(H^4–H^3) 10.9 Hz], 6.09 d.d (1H, HCF_2, $^2J_{H–F(A)}$ 55.1, $^2J_{H–F(B)}$ 54.6 Hz), 6.53 d [1H, H^1, J(H^1–OH) 0.5 Hz], 6.74 s (1H, H^6), 7.51 br.d [1H, CO_2H, J(CO_2H–H^3) 3.3 Hz], 7.56 d [1H, OH, J(OH–H^1) 0.5 Hz], 7.65–7.74 m (5H, C_6H_5). ^{19}F NMR spectrum, δ, ppm: 29.03 d.d (1F, CF_2, $J_{F(A)–F(B)}$ 282.8, $J_{F(A)–H}$ 54.6 Hz), 34.16 d.d (1F, CF_2, $J_{F(B)–F(A)}$ 282.8, $J_{F(B)–H}$ 55.1 Hz). Found, %: C 53.28; H 4.37; F 9.36; N 10.73. $C_{17}H_{17}F_2N_3O_5$. Calculated, %: C 53.54; H 4.49; F 9.96; N 11.02.

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REFERENCES

1. *Comprehensive Organic Chemistry*, Barton, D. and Ollis, W.D., Eds., Oxford: Pergamon, 1985, vol. 8.
2. Ulomskii, E.N., Shestakova, T.S., Deev, S.L., Rusinov, V.L., and Chupakhin, O.N., *Izv. Akad. Nauk, Ser. Khim.,* 2005, p. 713.
3. Pryadeina, M.V., Burgart, Ya.V., Saloutin, V.I., Kodess, M.I., Ulomskii, E.N., and Rusinov, V.L., *Zh. Org. Khim.,* 2004, vol. 40, p. 938.
4. Kappe, C.O., Falsone, S.F., Fabian, W.M.F., and Belaj, F., *Heterocycles*, 1994, vol. 51, p. 77.
5. Burgart, Ya.V., Kuzueva, O.G., Pryadeina, M.V., Kappe, S.O., Saloutin, V.I. ., *Zh. Org. Khim.,* 2001, vol. 37, p. 915.
6. Ionin, B.I., Ershov, B.A., and Kol'tsov, A.I., *YaMR-spektroskopiya v organicheskoi khimii* (NMR Spectroscopy in Organic Chemistry), Leningrad: Khimiya, 1983, p. 154.
7. Potapov, V.M., *Stereokhimiya* (Stereochemistry), Moscow: Khimiya, 1988, p. 211.
8. Pretsch, E., Bühlmann, P., and, Affolter, C., *Structure Determination of Organic Compounds: Tables of Spectral Data,* Springer, 2004.
9. Pryadeina, M.V., Burgart, Ya.V., Kodess, M.I., and Saloutin, V.I., *Izv. Akad. Nauk, Ser. Khim.,* 2005, p. 2745.
10. Atwal, K.S. and Moreland, S., *Bioorg. Med. Chem. Lett*., 1991, vol. 1, p. 291.
11. Sheldrick, G.M., *SHELXS 97*, University of Gцttingen, Germany, 1997.
12. Pryadeina, M.V., Kuzueva, O.G., Burgart, Ya.V., Saloutin, V.I., Lyssenko, K.A., and Antipin, M.Yu., *J. Fluor. Chem.,* 2002, vol. 117, p. 1.