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Fluorocontaining 1,3-Dicarbonyl Compounds in the Synthesis of Pyrimidine Derivatives

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Abstract—Hexafluoroacetylacetone reacts with urea (thiourea) to yield respectively 4,6-bis(hydroxy)-4,6-bis(trifluoromethyl)hexahydropyrimidin-2-one(thione). The dehydration of the products and also reaction of nonsymmetrical fluoroalkyl-containing 1,3-diketones with urea (thiourea) afford substituted pyrimidines. The condensation of fluorinated 3-oxoesters and 1,3-diketones with benzaldehyde and urea (thiourea) results in 5-alkoxycarbonyl(acyl)-4-hydroxy-2-oxo(thioxo)-6-phenyl-4-fluoroalkylhexahydropyrimidines that on dehydration furnish 5-alkoxycarbonyl(acyl)-2-oxo(thioxo)-4-phenyl-6-fluoroalkyltetrahydropyrimidines. Ethyl 7-nonafluorobutyl-5-phenyl-2,3-dihydrothiazolo[3,2-a]pyrimidine-6-carboxylate hydrobromide forms in reaction of dibromoethane with ethyl ether of 2-thioxo-4-phenyl-6-nonafluorobutyltetrahydropyrimidine.

Pyrimidines and their derivatives play important part in the functions of the human body. Pyrimidine structural fragment is included into quite a number of natural substances (nucleic acids, vitamin B_1), into synthetic medicinals (barbiturates), into chemotherapeutic preparations (fluorouracil) [1]. The biological activity of pyrimidine derivatives attracts great interest to their synthesis. In preparation of pyrimidines are widely used reactions of 1,3-dicarbonyl compounds (e.g. ethyl acetoacetate, acetylacetone) with urea, thiourea, guanidine etc [1]. An alternative way of building up pyrimidine molecules proceeding from 1,3-dicarbonyl compounds is Biginelli reaction, cyclocondensation of 3-oxoester with aldehydes and compounds of urea type [2].

We report here on the synthesis of pyrimidine derivatives proceeding from fluoroalkyl-containing 1,3-diketones (**I**) and 3-oxoesters (**II**). Whereas the reactions of fluorinated 3-oxoesters with compounds of urea type are relatively well studied [3], the data on such processes involving 1,3-diketones are limited to interactions of nonsimmetrical trifluoromethyl-substituted 1,3-diketones with urea [4]. In [5] the isolation of pyrimidines from the reaction products of fluoroalkyl-containing 1,3-diketones and urea was considered impossible. In Biginelli condensation was tested only ethyl trifluoroacetoacetate [6, 7].

We found that at boiling in ethanol hexafluoroacetylacetone (**Ia**) reacted with urea and thiourea to afford the corresponding hexahydropyrimidines **IIIa, b** (Scheme 1, Tables 1, 2). Note that these processes occur both in the presence of catalytic quantities of hydrochloric acid and with no acid catalyst. Formerly in [8] was stated that no reaction between hexafluoroacetylacetone with urea was possible.

Hexahydropyrimidines **IIIa, b** can exist as two diastereomers (*cis*- and *trans*-isomers).

The character of the resonance in the ^{1}H NMR spectrum of compound **IIIa** of nonequivalent diastereotopic methylene protons appearing as an AB-system with the geminal coupling constant 13.7 Hz (Table 2) and a single singlet peak of the trifluoromethyl group in the ^{19}F NMR spectrum evidence that heterocycle **IIIa** is present exclusively as *cis*-isomer.

In the ^{1}H and ^{19}F NMR spectra of compound **IIIb** appear two sets of signals indicating the presence of two isomers (Table 2). The methylene protons signals in the ^{1}H NMR spectrum (AB-system with the coupling constant 13.9 Hz for the *cis*-isomer and a broadened singlet for the trans-isomer) distinguish the isomers and permit evaluation of their ratio. Thus unlike the carbonyl analog **IIIa** hexahydropyrimidine-2-thione (**IIIb**) exists as *cis*- and *trans*-isomers mixture in 3 : 1 ratio. We failed to separate the isomers and isolate them in a pure state.

To establish the position of the fluoroalkyl group in the cis-isomer we take into account the known fact that the substituent of higher conformational energy displaces the neighboring group into the axial position

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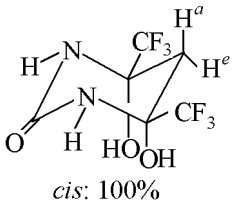
Table 1. Elemental analysis of compounds **IIIa, b, IVa–d, Va–h, VIa–i, VIIIa, b, IXa, b, X**

Compd. no.	Found, %					Formula	Calculated, %				
	C	H	F	N	S		C	H	F	N	S
IIIa	26.98	2.31	42.62	10.45		$C_6H_6F_6N_2O_3$	26.88	2.26	42.51	10.45	
IIIb	25.28	2.05	40.16	10.17	11.28	$C_6H_6F_6N_2O_2S$	25.36	2.13	40.11	9.86	11.28
IVa	31.05	0.83	49.32	11.90		$C_6H_2F_6N_2O$	31.05	0.87	49.11	12.07	
IVb	29.21	1.09	45.91	11.36		$C_6H_2F_6N_2S$	29.04	0.81	45.94	11.29	
IVc	52.91	2.67	27.73	10.00		$C_{12}H_8F_4N_2O$	52.95	2.96	27.92	10.29	
IVd	37.20	2.76	33.17	12.20	13.95	$C_7H_6F_4N_2S$	37.17	2.67	33.60	12.38	14.17
Va	59.39	5.17	12.44	8.65		$C_{14}H_{16}F_2N_2O_4$	53.50	5.13	12.09	8.91	
Vb	48.13	4.16	22.14	8.06		$C_{14}H_{14}F_4N_2O_4$	48.00	4.03	21.70	8.00	
Vc	43.25	3.14	31.91	6.70		$C_{15}H_{13}F_7N_2O_4$	43.07	3.13	31.80	6.70	
Vd	42.34	3.13	35.45	5.81		$C_{17}H_{15}F_9N_2O_4$	42.29	3.21	35.53	5.96	
Ve	46.21	4.12	20.38	7.65	8.65	$C_{14}H_{14}F_4N_2O_3S$	45.90	3.85	20.74	7.65	8.75
Vf	41.45	3.23	30.62	6.68	7.34	$C_{15}H_{13}F_7N_2O_3S$	41.48	3.02	30.62	6.42	7.38
Vg	40.98	3.13	34.26	5.67	6.48	$C_{17}H_{15}F_9N_2O_3S$	40.97	3.03	34.21	5.62	6.43
Vh	48.18	4.32	16.34	8.01		$C_{14}H_{15}F_3N_2O_3S$	48.27	4.34	16.36	8.04	
VIa	57.44	4.12	19.12	7.04		$C_{19}H_{16}F_4N_2O_3$	57.58	4.07	19.17	7.07	
VIb	50.39	4.27	22.74	8.43		$C_{14}H_{14}F_4N_2O_3$	50.30	4.22	22.73	8.38	
VIc	51.49	4.28	18.85	9.28		$C_{13}H_{13}F_3N_2O_3$	51.66	4.34	18.86	9.27	
VId	59.23	4.05	15.69	7.54		$C_{18}H_{15}F_3N_2O_3$	59.34	4.15	15.64	7.69	
VIe	55.25	4.06	18.54	6.69	7.70	$C_{19}H_{16}F_4N_2O_2S$	55.34	3.91	18.43	6.79	7.77
VIf	49.05	4.14	17.83	8.78	10.14	$C_{13}H_{13}F_3N_2O_2S$	49.05	4.12	17.91	8.80	10.07
VIg	56.95	3.84	14.76	7.36	8.47	$C_{18}H_{15}F_3N_2O_2S$	56.84	3.97	14.98	7.36	8.43
VIh	43.74	2.82	32.14	7.93		$C_{13}H_{10}F_6N_2O_3$	43.83	2.83	32.00	7.86	
VIi	41.99	2.75	30.74	7.56	8.35	$C_{13}H_{10}F_6N_2O_2S$	41.94	2.71	30.62	7.52	8.61
VIIIa	43.93	2.86	36.91	6.14		$C_{17}H_{13}F_9N_2O_3$	43.98	2.82	36.83	6.03	
VIIIb	42.68	2.79	35.62	5.87	6.67	$C_{17}H_{13}F_9N_2O_2S$	42.51	2.73	35.60	5.83	6.67
IXa	60.07	3.68	19.85	7.50		$C_{19}H_{14}F_4N_2O_2$	60.32	3.73	20.09	7.40	
IXb	57.70	3.52	19.04	7.04		$C_{19}H_{14}F_4N_2OS$	57.86	3.58	19.27	7.10	
X	38.85	2.74	29.13	4.75	5.48	$C_{19}H_{15}F_9N_2O_2S$–HBr	38.86	2.75	29.11	4.77	5.46

[9]. Therefore trifluoromethyl group (ΔG 8.8 kJ mol^{-1}) takes the equatorial position, and the hydroxy group (ΔG 2.2 kJ mol^{-1}) the axial one (Figs. 1, 2).

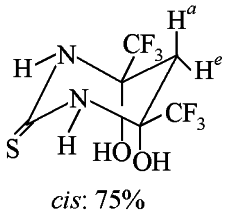
Both literature data [4] and our own experiments show that unlike hexafluoroacetylacetone (**Ia**) the nonsymmetrical 1,3-diketones with a single fluorinated substituent **Ib, c** react with urea and thiourea at boiling in ethanol in the presence or in the absence of acid catalyst to afford pyrimidines **IVc, d** (Scheme 1, Tables 1, 2).

Pyrimidines **IVa, b** with two trifluoromethyl substituents can only be obtained from the, corresponding hexahydropyrimidines **IIIa, b** by boil-

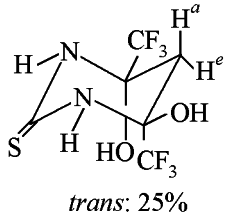


cis: 100%

Fig. 1. Conformational structure of 4,6-bis(hydroxy)-4,6-bis(trifluoromethyl)hexahydropyridin-2-one (**IIIa**).



cis: 75%



trans: 25%

Fig. 2. Conformational structure of 4,6-bis(hydroxy)-4,6-bis(trifluoromethyl)hexahydropyridine-2-thione (**IIIb**).

Table 2. Yields, melting points, and spectral characteristics of compounds **IIIa, b, IVa–d, Va–h, VIa–i, VIIIa, b, IXa, b, X**)

Compd. no.	mp, °C	Yield, %	IR spectrum, ν, cm^{-1}
IIIa	211–212	82 (*a*), 44 (*b*), 36 (*c*)	3290, 3130, 1590 (NH, OH), 1660 (C=O amide), 1200–1140 (C–F)
IIIb	164–165	56	3290, 3180, 1555 (NH, OH), 3080 (C–H stretch.), 1230–1150 (C–F)
IVa	133–135	68	3290, 3210, 3120, 1620 (NH), 1665 (C= amide), 1580 (C=C, C=N conjug.), 1290–1150
IVb	50–51	62	(C–F) 3090 (C–H stretch.), 1580, 1555 (C=N, C=C conjug.), 1300–1100 (C–F)
IVc	178–179	34	3320, 3140, 1600 (NH), 3070 (C–H stretch.), 1660 (C=O amide.), 1570 (C=C conjug.), 1240–1080 (C–F)
IVd[a]	136–137	32	3170–2870 (SH, C–H stretch.), 1585, 1560 (C=N, C=C conjug.)
Va	204–205	75	3315, 3200, 1585 (NH, OH), 3090 (C–H stretch.), 1720 (CO_2Et), 1665 (C=O), 1500 (C= conjug.), 1170–1070 (C–F)
Vb	190–192	79	3440, 3220, 1585 (NH, OH), 3055 (C–H stretch.), 1740 (CO_2CH_3), 1660 (C=O), 1500 (C=C conjug.), 1160–1090 (C–F)
Vc	204–205	73	3450, 3205, 1630 sh. (NH, OH), 3080 (C–H stretch.), 1740 (CO_2CH_3), 1670 (C=O), 1490 (C=C conjug.), 1230–1100 (C–F)
Vd	191–192	80	3420, 3190, 1620 sh. (NH, OH), 3075 (C–H stretch.), 1720 (CO_2Et), 1675 (C=O), 1630 sh (C=C conjug.), 1220–1090 (C–F)
Ve	212–213	50	3400, 3200, 1600 (NH, OH), 3090 (C–H stretch.), 1735 (CO_2CH_3), 1580, 1565, 1500 (C=C conjug.), 1220–1100 (C–F)
Vf	215–217	47	3440, 3200, 1600 (NH, OH), 3100 (C–H stretch.), 1740 (CO_2CH_3), 1585, 1565, 1490 (C=C conjug.), 1280–1170 (C–F)
Vg	212–213	45	3440, 3185, 1600 (NH, OH), 3100 (C–H stretch.), 1730 (CO_2Et), 1580, 1500 (C=C conjug.), 1230–1130 (C–F)
Vh	190–191	43	3430, 3190, 1600 (NH, OH), 3100 (C–H stretch.), 1735 (CO_2Et), 1570 (C=C conjug.), 1260–1170 (C–F)
VIa	233–234	38	3430, 3190, 1590 (NH, OH), 3050 (C–H stretch.), 1675 (C=O ket.), 1660 (C=O amide.), 1490 (C=C conjug.), 1140–1100 (C–F)
VIb	184–185	33	3450, 3390, 3210, 1590 (NH, OH), 3090 (C–H stretch.), 1700 (C=O ket.), 1690 (C=O amide), 1480 C=C conjug.), 1160–1110 (C–F)
VIc	180–182	32	3400, 3390, 3220, 1610 (NH, OH), 3080, 3050 (C–H stretch.), 1720, 1705 (C=O ket.), 1680, 1660 (C=O amide), 1500 (C=C conjug.), 1190–1170 (C–F)
VId	204–205	42	3430, 3190, 1590 (NH, OH), 3060 (C–H stretch.), 1675 (C=O ket.), 1660 (C=O amide), 1500 (C=C conjug.), 1200–1175 (C–F)
VIe	233–234	36	3440, 3190, 1595 (NH, OH), 3100 (C–H stretch.), 1680 (C=O ket.), 1560, 1500 (C=C conjug.), 1220–1150 (C–F)
VIf	211–212	22	3380, 3260, 3160, 1580 (NH, OH), 3050 (C–H stretch.), 1690 (C=O ket.), 1550, 1500 (C=C conjug.), 1240–1160 (C–F)
VIg	229–230	30	3430, 3180, 1585 (NH, OH), 3090 (C–H stretch.), 1665 (C=O ket.), 1560, 1500 (C=C conjug.), 1250–1120 (C–F)
VIh	200–201	30	3390, 3200, 1610 (NH, OH), 3060 (C–H stretch.), 1745 (C=O ket.), 1660 (C=O amide), 1480 (C=C conjug.), 1200–1100 (C–F)
VIi	215–216	20	3160, 1580 (NH, OH), 3100 (C–H stretch.), 1740 (C=O ket.), 1560, 1510 (C=C conjug.), 1200–1170 (C–F)
VIIIa	154–155	56	3270, 3210, 1650 sh. (NH), 3080 (C–H stretch.), 1730 (CO_2Et), 1690 (C=O ket.), 1670 (C=C conjug.), 1240–1140 (C–F)
VIIIb	137–138	48	3295, 3180, 1580 sh. (NH), 3100 (C–H stretch.), 1710 (CO_2Et), 1670 (C=O amide.), 1560 (C=C conjug.), 1220–1130 (C–F)
IXa	152–153	44	3235, 1600 (NH), 3100 (C–H stretch.), 1710 (C=O ket.), 1675 (C=O amide.), 1660 (C=C=C), 1490(C=C conjug.), 1170–1100 (C–F)
IXb	123–124	40	3150, 1590 (NH), 3090 (C–H stretch.), 1665 (C=O ket.), 1650 (C=C), 1570 (C=C conjug.), 1210–1100 (C–F)
X[b]	218–220	42	2770, 2745, 2700 (N^+H), 1730 (CO_2Et), 1660, 1500 (C=C, C=N conjug.), 1240–1140 (C–F)

Table 2. (Contd.)

Compd. no.	^{1}H NMR spectrum, δ, ppm, *J*, Hz	^{19}F NMR spectrum, δ_F, ppm, *J*, Hz
IIIa	2.15 m (2H, $H^{5a}H^{5e}$, *AB*-system, Δν 18.28, *J* 13.7), 6.94 7.97 2s (4H, 2NH, 2OH)	78.60 s (6F, $2CF_3$)
IIIb	*cis/trans* 3/1 *cis*: 2.21 m (2H, $H^{5a}H^{5e}$, *AB*-system, Δν 24.00, *J* 13.9), 7.32, 9.50 2s (4H, 2NH, 2OH) *trans*: 2.38 s (2H, $H^{5a}H^{5e}$), 7.38, 9.24 2s (4H, 2NH, 2OH)	*cis/trans* 3/1 *cis*: 79.56 s (6F, $2CF_3$) *trans*: 80.52 s (6F, $2CF_3$)
IVa	7.91 s (1H, H^5), 13.74 br.s (1H, NH)	93.65 s ($2CF_3$)
IVb	7.21 br.s (1H, SH), 8.48 s (1H,H^5)	93.72 s ($2CF_3$)
IVc	6.88 t.t [1H. $H(CF_2)_2$, $^2J_{HF}$ 51.8, $^3J_{HF}$ 5.6], 7.62 s (1H, H^5), 7.54–8.21 m (5H, C_6H_5), 12.77 br.s (1H, NH)	24.37 d.t (2F, HCF_2CF_2, $^2J_{FH}$ 51.8, $^3J_{FF}$ 7.9), 42.36 m (2F, HCF_2CF_2, $^3J_{FF}$ 7.9, $^3J_{FH}$ 5.6)
IVd[a]	2.61 s (3H, CH_3), 6.65 t.t [1H, $H(CF_2)_2$, $^2J_{HF}$ 51.6, $^3J_{HF}$ 6.0], 7.13 s (1H, H^5), 11.40 br.s (1H, SH)	
Va	0.87 t (3H, OCH_2CH_3, *J* 7.0), 2.92 d (1H, H^5, *J* 11.6), 3.82 q (2H, OCH_2CH_3, *J* 7.0), 4.80 d (1H, H^6, *J* 11.6), 5.88 t (1H, HCF_2, J_{HF} 55.2), 7.33 s (5H, C_6H_5), 6.67, 7.00, 7.15 3s (3H, 2NH, OH)	30.38 m (2F, HCF_2, *AB*-system, Δν 236.0, $^2J_{FF}$ 274.9, $^2J_{FH}$ 55.2)
Vb	3.00 d (1H, H^5, *J* 11.1), 3.27 s (3H, OCH_3), 4.79 d (1H, H^6, *J* 11.1), 6.70 t.t [1H, $H(CF_2)_2$, $^2H_{HF}$ 51.4, $^3J_{HF}$ 5.1], 7.32 s (5H, C_6H_5), 7.10 s (1H, OH), 7.20 s (2H, 2NH)	27.57 m (2F, HCF_2CF_2, *AB*-system), 35.14 m (2F, HCF_2CF_2, *AB*-system, Δν 166.12, $^2J_{FF}$ 266.0)
Vc	3.04 d (1H, H^5, *J* 11.0), 3.28 s (3H, OCH_3), 4.81 d (1H, H^6, *J* 11.0), 7.33 s (5H, C_6H_5), 7.17, 7.53, 7.61 3s (3H, 2NH, OH)	40.39 m (2F, CF_2), 43.76 m (2F, CF_2), 82.26 m (3F, CF_3)
Vd	0.78 t (3H, OCH_2CH_3, *J* 7.1), 3.03 d (1H, H^5, *J* 11.1), 3.74 q (2H, OCH_2CH_3, *J* 7.1), 4.81 d (1H, H^6, *J* 11.1), 7.33 s (5H, C_6H_5), 5.39, 7.11, 7.48 3s (3H, 2NH, OH)	37.25 m (2F, CF_2), 44.66–43.51 m (4F, $2CF_2$), 82.42 m (3F, CF_3)
Ve	3.09 d (1H, H^5, *J* 11.7), 3.28 s (3H, OCH_3), 4.81 d (1H, H^6, *J* 11.7), 6.79 t.t [1H, $H(CF_2)_2$, $^2J_{HF}$ 51.4, $^3J_{HF}$ 6.6], 7.33 c (5H, C_6H_5), 7.73, 8.31, 9.19 3s (3H, 2NH, OH)	27.46 m (2F, HCF_2CF_2, *AB*-system), 35.76 m (2F, HCF_2CF_2, *AB*-system)
Vf	3.14 d (1H, H^5, *J* 11.3), 3.30 s (3H, OCH_3), 4.83 d (1H, H^6, *J* 11.3), 7.34 s (5H, C_6H_5), 8.13, 9.35 2s (3H, 2NH, OH)	40.38 m (2F, CF_2), 44.05 m (2F, CF_2), 82.35 m (3F, CF_3)
Vg	0.81 t (3H, OCH_2CH_3, *J* 7.1), 3.13 d (1H, H^5, *J* 11.5), 3.78 q (2H, OCH_2CH_3, *J* 7.1), 4.84 d (1H, H^6, *J* 11.5), 7.35 s (5H, C_6H_5), 7.90, 7.98, 9.24 3s (3H, 2NH, OH)	37.08 m (2F, CF_2), 43.73 m (2F, CF_2), 44.86 m (2F, CF_2), 82.33 m (3F, CF_3)
Vh	0.81 t (3H, OCH_2CH_3, *J* 7.1), 3.02 d (1H, H^5, *J* 11.8), 3.79 q (2H, OCH_2CH_3, *J* 7.1), 4.79 d (1H, H^6, *J* 11.8), 7.34 s (5H, C_6H_5), 7.88, 8.89, 9.09 3s (3H, 2NH, OH)	82.30 s (CF_3)
VIa	4.65 m (2H, H^5H^6, *AB*-system, Δν 47.45, *J* 11.0), 6.72 t.t [1H, $H(CF_2)_2$, $^2J_{HF^{1,2}}$ 51.3, $^3J_{HF^{3,4}}$ 6.7], 7.04–7.46 m (10H, $2C_6H_5$), 7.54, 7.62 2s (3H, 2NH, OH)	27.79 · (2F, HCF_2CF_2, *AB*-system, Δν 159.34, $^2J_{F^1F^2}$ 300.0, $^2J_{F^{1,2}H}$ 51.3, $^3J_{F^{1,2}F^{3,4}}$ 7.6), 38.11 m (2F, HCF_2CF_2, *AB*-system)
VIb	1.80 s (3H, CH_3), 3.10 d (1H, H^5, *J* 11.4), 4.82 d (1H, H^6, *J* 11.4), 6.71 t.t [1H, $H(CF_2)_2$, $^2J_{HF^{1,2}}$ 51.5, $^3J_{HF^{3,4}}$ 6.8], 7.21, 7.28 2s (3H, 2NH, OH), 7.34 s (5H, C_6H_5)	27.64 m (2F, HCF_2CF_2, *AB*-system), 36.69 m (2F, HCF_2CF_2, *AB*-system, Δν 116.83, $^2J_{F^3F^4}$ 267.0, $^3J_{F^{3,4}H}$ 6.8, $^3J_{F^{3,4}F^{1,2}}$ 7.6)
VIc	1.88 s (3H, CH_3), 3.11 d (1H, H^5, *J* 11.6), 4.84 d (1H, H^6, *J* 11.7), 7.35 s (5H, C_6H_5), 7.19, 7.52, 7.61 3s (3H, 2NH, OH)	82.04 s (CF_3)
VId	4.68 m (2H, H^5H^6, *AB*-system, Δν 47.94, *J* 11.1), 7.10–7.40 m (10H, $2C_6H_5$), 7.60, 7.72 2s (3H, 2NH, OH)	82.71 s (CF_3)
VIe	4.72 m (2H, H^5H^6, *AB*-system, Δν 41.79, *J* 11.5), 6.84 t.t [1H, $H(CF_2)_2$, $^2J_{HF^{1,2}}$ 51.5, $^3J_{HF^{3,4}}$ 6.0], 7.09–7.58 m (10H, $2C_6H_5$), 7.66, 8.30, 9.20 3s (3H, 2NH, OH)	27.50 m (2F, HCF_2CF_2, *AB*-system), 38.65 m (2F, HCF_2CF_2, *AB*-system, Δν 80.22, $^2J_{F^3F^4}$ 264.4, $^3J_{F^{3,4}H}$ 6.0, $^3J_{F^{3,4}F^{1,2}}$ 7.3)

Table 2. (Contd.)

Compd. no.	^{1}H NMR spectrum, δ, ppm, *J*, Hz	^{19}F NMR spectrum, δ_F, ppm, *J*, Hz
VIf	1.89 s (3H, CH_3), 3.19 d (1H, H^5, *J* 11.8), 4.86 d (1H, H^6, *J* 11.8), 7.35 s (5H, C_6H_5), 8.02, 8.96, 9.09 3s (3H, 2NH, OH)	82.90 s (CF_3)
VIg	4.75 m (2H, H^5H^6, *AB*-system, Δν 38.80, *J* 11.5), 7.15–7.70 m (10H, $2C_6H_5$), 7.75, 8.95, 9.09 3s (3H, 2NH, OH)	83.61 c (CF_3)
VIh	3.83 d (1H, H^5, *J* 11.5), 4.88 d (1H, H^6, *J* 11.5), 7.34 s (5H, C_6H_5), 7.44, 7.95, 8.09 3s (3H, 2NH, OH)	81.17 q (3F, CF_3, *J* 5.3), 84.03 q (3F, CF_3, *J* 5.3)
VIi	3.97 d (1H, H^5, *J* 11.5), 4.89 d (1H, H^6, *J* 11.5), 7.35 s (5H, C_6H_5), 8.38, 9.29, 9.46 3s (3H, 2NH, OH)	82.59 q (3F, CF_3, *J* 5.4), 84.59 q (3F, CF_3, *J* 5.4)
VIIIa	1.03 t (3H, $OCH_2\underline{CH_3}CH_3$, *J* 7.1), 4.00 q (2H, $O\underline{CH_2}CH_3$, *J* 7.1), 5.25 br.s (1H, H^4), 7.34 m (5H, C_6H_5), 7.96 br.s (1H, NH), 9.60 s (1H, NH)	36.92 m (2F, CF_2), 42.85 m (2F, CF_2), 52.62 m (2F, CF_2), 82.25 m (3F, CF_3)
VIIIb	1.08 t (3H, $OCH_2\underline{CH_3}$, *J* 7.1), 4.07 q (2H, $O\underline{CH_2}CH_3$, *J* 7.1), 5.25 d (1H, H^4, ^3J 3.1), 7.21–7.46 m (5H, C_6H_5), 9.20 d (1H, NH, ^3J 3.1), 10.71 s (1H, NH)	36.85 m (2F, CF_2), 42.88 m (2F, CF_2), 52.86 m (2F, CF_2), 82.19 m (3F, CF_3)
IXa	5.13 br.s (1H, H^4), 6.65 m [1H, $H(CF_2)_2$, $^2J_{HF^{1,2}}$ 52.0, $^3J_{HF^3}$ 7.4, $^3J_{HF^4}$ 4.6], 7.18–7.65 m (10H, $2C_6H_5$), 7.86, 9.43 2 br.s (2H, 2NH)	25.08 d.t (2F, $H\underline{CF_2}CF_2$, $^2J_{F^{1,2}H}$ 52.0, $^3J_{F^{1,2}F^{3,4}}$ 7.9), 46.04 m (2F, $HCF_2\underline{CF_2}$, *AB*-system, Δν 363.30, $^2J_{F^3F^4}$ 269.6, $^3J_{F^{3,4}F^{1,2}}$ 7.9, $^3J_{F^3H}$ 7.4, $^3J_{F^4H}$ 4.6)
IXb	5.10 br.s (1H, H^4), 6.76 t.t [1H, $H(CF_2)_2$, $^2J_{HF}$ 51.9, $^3J_{HF}$ 6.0], 7.20–7.67 m (10H, $2C_6H_5$), 9.70, 10.67 2 br.s (2H, 2NH)	24.75 m (2F, $H\underline{CF_2}CF_2$, *AB*-system), 46.90 m (2F, $\underline{HCF_2}\underline{CF_2}$, *AB*-system)
X[b]	1.11 t (3H, $OCH_3\underline{CH_3}$, *J* 7.0), 3.71 m (2H, $H^{2a}H^{2e}$, *J* 6.5), 4.17 q (2H, $O\underline{CH_2}CH_3$, *J* 7.0), 4.58 m (2H, $H^{3a}H^{3e}$, *J* 6.5), 5.92 s (1H, H^5), 7.50 m (5H, C_6H_5)	

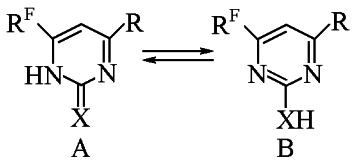
[a] ^{1}H NMR spectrum of compound **IVd** was recorded in acetone-d_6.

[b] ^{1}H NMR spectrum of compound **X** was recorded in CF_3COOD.

ing the latter in toluene in the presence of *p*-toluenesulfonic acid while eliminating the arising water with azeotrope (Scheme 1, Tables 1, 2).

Fluoroalkyl-containing 2-mercaptopyrimidines, in particular heterocycle **IVd**, were prepared before from lithium salts of 1,3-diketones [5], and the possibility to obtain the compounds from the free ligands was deemed impossible.

Compounds **IVa–d** may undergo lactam-lactim tautomerism. These compounds can exist as dihydropyrimidine-2-one(thione) (**A**) or as 2-hydroxy-(mercapto)pyrimidine (**B**), or as a tautomers mixture.



A B

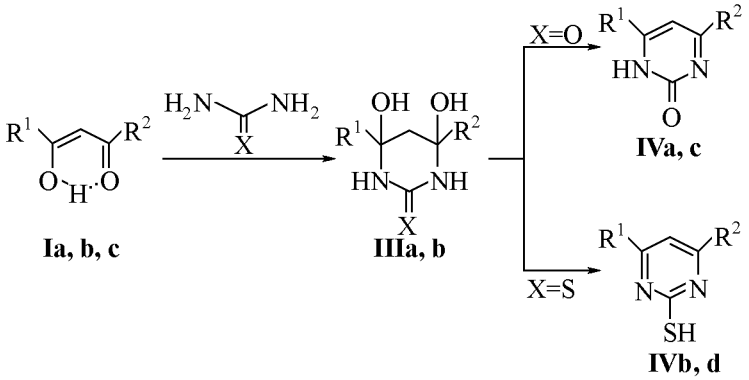
X = O, S.

However in the ^{1}H and ^{19}F NMR spectra appears a single set of signals (Table 2) indicating that compounds **IVa–d** exist as one of the possible tautomers. Analysis of the IR spectra of compounds **IVa, c** where are present strong bands at 3440–3120 cm^{-1} characteristic of amino group stretching vibrations, and also absorption bands at 1670–1660 cm^{-1} corresponding to carbonyl group of amide moiety suggest that the lactam structure of the heterocycles is more favored.

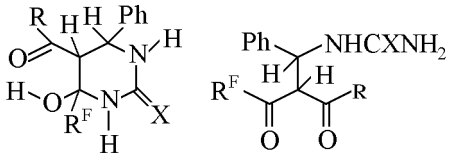
Since in the IR spectra of compounds **IVb, d** the vibration bands of amino groups in the high frequency region are lacking and since the thiocarbonyl compounds are known to be prone to tautomeric transformations [10] compounds **IVb, d** apparently exist as pyrimidine **B**. We did not succeed in more definite assignment of the pyrimidine structure.

The study of Biginelli condensation in the series of fluoroalkyl-containing 1,3-dicarbonyl compounds revealed that in contrast to the nonfluorinated analogs the fluoro-containing 3-oxoesters **IIa–e** and 1,3-diketones **Ib–e** at boiling with urea or thiourea and

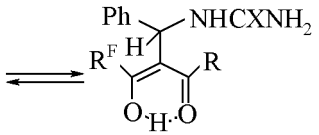
Scheme 1.



benzaldehyde in ethanol in the presence of catalytic amounts of hydrochloric acid in 5–6 h give rise to compounds **Va–h**, **VIa–g** (Scheme 2, Tables 1, 2). These products may have either a structure of cyclic hexahydropyrimidine (**C**) or open-chain derivative of ureidopropionate (**D**). The elemental analyses of these compounds are identical. The latter substance is prone to keto-enol tautomerism and thus it may exists enol (**De**), ketone (**Dk**), or as tautomers mixture.



C **Dk**



De

A single set of signals in the ^1H and ^{19}F NMR spectra of compounds **Va–h, VIa–g** (Table 2) evidences that the substances exist in a single structural form.

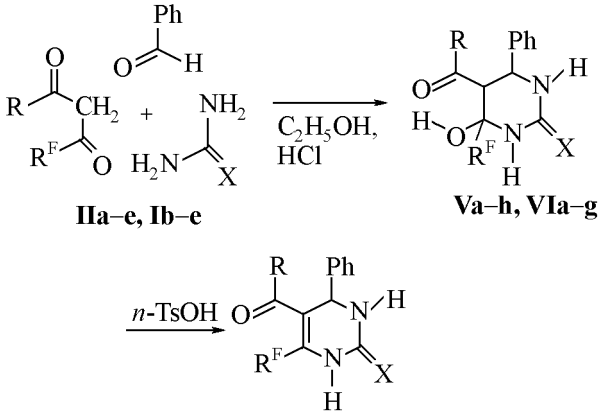
In [7] was described the formation of an open-chain ureidopropionate (**Dk**, $R^f=CF_3$, R=OEt) in reaction of ethyl trifluoroacetylacetate, benzaldehyde, and thiourea. Compound **Vh** that we isolated after this reaction had a melting point and spectral characteristics similar to those published in [7].

In the IR spectra of compounds **Va–h, VIa–g** are lacking two narrow absorption bands corresponding to asymmetrical and symmetrical stretching vibrations of NH_2 belonging to **Dk, De** structures and a weak band from enol hydroxy group of **De** form. At the same time in the spectra appear strong broadened absorption bands of hydroxy substituent at 3450–3315 cm^{-1} in **C** structure.

The presence in the ^1H NMR spectra of compounds **Va–h**, **VIa–g** ot two doublets corresponding to two methine protons (2.92–4.89 ppm) totally excludes the enol structure **De**. The calculated coupling constants (J 11–11.8 Hz) confirm the cyclic structure of the products since the vicinal coupling constants for open-chain saturated hydrocarbons are commonly equal to 6–8 Hz [11].

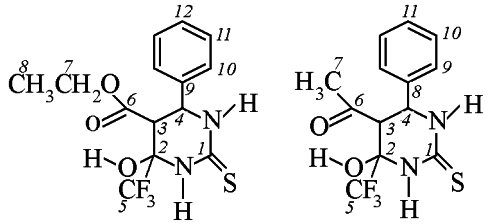
The cyclic structure of compound **Vh** described in [7] as ureidopropionate was finally proved by ^{13}C NMR spectroscopy: In the spectrum was present

Scheme 2.



R^F = HCF_2, R = OEt (**IIa**) X = O (**Va**); R^F = $H(CF_2)_2$, R = OMe (**IIb**), X = O (**Vb**), S (**Ve**); R^F = C_3F_7, R = OMe (**IIc**), X = O (**Vc**), S (**Vf**); R^F = C_4F_9, R = OEt (**IId**), X = O (**Vd, VIIIa**), S (**Vg, VIIIb**); R^F = CF_3, R = OEt (**IIe**), X = S (**Vh**); R^F = $H(CF_2)_2$, R = Ph (**Ib**), X = O (**VIa, IXa**), S (**VIe, IXb**); R^F = $H(CF_2)_2$, R = Me (**Ic**), X = O (**VIb**); R^F = CF_3, R = Me (**Id**), X = O (**VIc**), S (**VIf**); R^F = CF_3, R = Ph (**Ie**), X = O (**VId**), S (**VIg**).

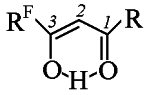
Table 3. ^{13}C NMR spectra, δ_C, ppm [$J(^{13}C—^{19}F)$, Hz] of compounds **Vh, VIc** in DMSO-d_6



Vh **VIc**

Compd. no.	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}	C^{11}	C^{12}
Vh	177.17	79.61 (31.13)	54.30	60.37	122.84 (288)	166.40	49.36	13.36	136.89	128.06	128.31	128.55
VIc	164.22	80.69 (30.52)	53.21	57.21	123.21 (288)	203.89	30.58	153.72	127.97	128.52	138.04	

Table 4. Charges and Fukui indices on the reaction centers of 1,3-diketones (**Ib**–**e**) and 3-oxoesters **IIa**–**e**

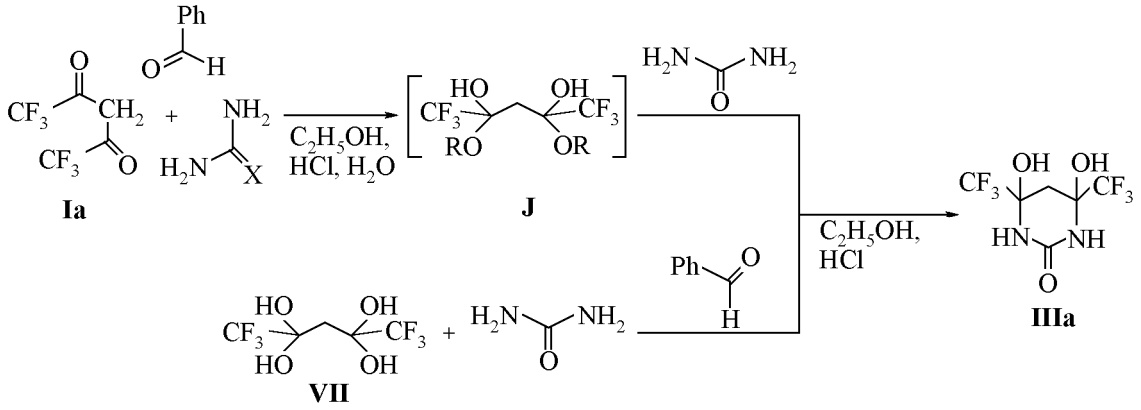


Compd. no.	R^F	R	Charges (Fukui indices for HOMO/Fukui indices for LUMO)		
			C^1	C^2	C^3
Ib	$H(CF_2)_2$	Ph	+0.4023 (0.0000/0.1937)	–0.3474 (0.0559/0.0639)	+0.1170 (0.0227/0.2147)
Ic	$H(CF_2)_2$	Me	+0.3503 (0.0004/0.1899)	–0.3474 (0.4799/0.1681)	+0.1162 (0.1912/0.3830)
Id	CF_3	Me	+0.3501 (0.0003/0.1892)	–0.3401 (0.4748/0.1770)	+0.1085 (0.1937/0.3912)
Ie	CF_3	Ph	+0.4018 (0.0000/0.1960)	–0.3389 (0.0124/0.0737)	+0.1095 (0.0052/0.2279)
IIa	HCF_2	OEt	+0.4418 (0.0004/0.1619)	–0.3004 (0.4848/0.1979)	+0.1015 (0.1960/0.4181)
IIb	$H(CF_2)_2$	OMe	+0.4362 (0.0003/0.1491)	–0.2891 (0.4791/0.2082)	+0.1036 (0.1985/0.4134)
IIc	C_3F_7	OMe	+0.4354 (0.0002/0.1043)	–0.2846 (0.4745/0.1896)	+0.1003 (0.1938/0.3295)
IId	C_4F_9	OEt	+0.4405 (0.0001/0.1368)	–0.2822 (0.4724/0.2230)	+0.1054 (0.1980/0.4124)
IIe	CF_3	OEt	+0.4411 (0.0001/0.1440)	–0.2920 (0.4754/0.2161)	+0.1036 (0.1921/0.4220)

a quartet signal of carbon atom attached to the trifluoromethyl group ($^2J_{C-F}$ 31.1 Hz) in the region characteristic of quaternary carbons [12] (Table 3).

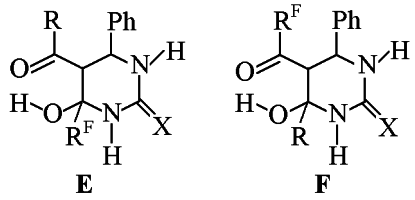
Thus the combined IR and NMR spectral data confirm the cyclic **C** structure of hexahydropyrimidine for the products of the above reactions. The hexahydropyrimidine structure of compounds **Va–h, VIa–g** may be considered as unambiguously determined, the more so as for the only earlier obtained trifluoromethyl-substituted analog it was solved by the X-ray diffraction analysis [6].

Scheme 3.



It should be noted that 2-methyl-substituted ethyl trifluoroacetylacetate does not enter into condensation with benzaldehyde and urea apparently due to steric hindrances.

At the use in the Biginelli reaction of nonsymmetrical 1,3-diketones as 3-oxoester component the cyclization



R^F = CF_3, $H(CF_2)_2$; R = Me, Ph.

into a pyrimidine ring may occur in two ways: The condensation can either proceed at the carbonyl group at the fluorinated substituent or at the carbonyl linked to the nonfluorinated radical affording respectively products **E** and **F** or their mixture.

The published data on condensation of nonsymmetrical 1,3-diketones with one fluorinated substituent with amines (ammonia, primary amines, polyalkylenepolyamines show that the reaction is predominantly directed on the carbonyl neighboring to the nonfluorinated radical [3]. This fact is due to induction of higher δ^+ on the remote carbonyl and not on that near the fluorinated substituent. The latter statement is supported by our quantum-chemical calculations (Table 4) performed by MNDO procedure [13]. According to calculations the highest positive charge in fluoroalkyl-containing 1,3-diketones **I** and 3-oxoesters **II** is located on C^1 carbon that in 1,3-diketones is linked to the nonfluorinated substituent, and in 3-oxoesters belongs to the ester moiety. Fukui indices for the lowest unoccupied molecular orbital (LUMO) in all compounds have the maximal value for C^3 carbon bonded to the fluorinated substituent. Therefore at the kinetic control of the process the predominant place of nucleophile attack should be C^1 atom due to the charge distribution; at the orbital control the reaction should occur at C^3.

The NMR spectra registered from compounds **VIa–g** contain a single set of signals. We chose for the compounds **E** structure basing on the ^{13}C NMR spectrum of compound **VIc**: In this spectrum the quartet signal from the carbon atom linked to the trifluoromethyl group ($^2J_{C-F}$ 30.52 Hz) appeared in the region characteristic of quaternary carbon and not of carbonyl carbon [12] as should have been in **F** structure (Table 3).

Thus the fluoroalkyl-containing 1,3-diketones in the Biginelli reaction behave as fluorinated 3-oxoesters affording substituted hexahydropyrimidines, and cyclocondensation occurs regioselectively at the carbonyl group adjacent to the fluoroalkyl substituent that corresponds to orbital and not charge control of the reaction. Unlike the above described reactions of 3-oxoesters **IIa–e** and 1,3-diketones **Ib–e** hexafluoroacetylacetone (**Ia**) in Biginelli reaction with benzaldehyde and urea at boiling in ethanol with hydrochloric acid as catalyst yields substituted hexahydropyrimidin-2-one **IIIa** (Scheme 3, Tables 1, 2). The structure of the latter compound results apparently from reaction competing with Biginelli condensation where hexafluoroacetylacetone reacts at both carbonyl groups with amino groups of urea without benzaldehyde participation.

A characteristic reaction of 1,3-diketones with two fluorinated substituents is water or alcohol addition at both carbonyl groups resulting in stable geminal adducts (tetraols and bis-semiketals) [3]. Obviously the hexafluoroacetylacetone under the reaction

conditions (in alcohol–water mixture) forms bis-semiketal (or tetraol) (**J**) that no more contains an activated methylene group and cannot react with benzaldehyde, only with urea to afford heterocycle **IIIa** (Scheme 3).

The assumed reaction path was indirectly supported by the behavior in Biginelli reaction of 2,2,4,4-tetrahydroxy-1,1,1,5,5,5-hexafluoropentane (**VII**) that we studied. As expected, tetraol **VII** did not react with benzaldehyde but condensed with urea to furnish hexahydropyrimidine **IIIa** (Scheme 3).

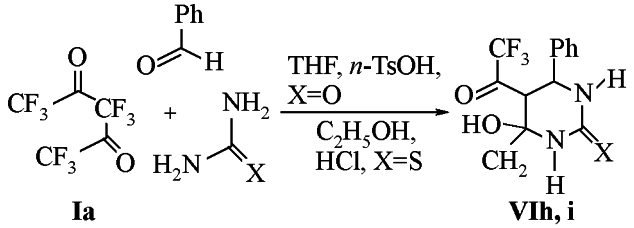
The assumed mechanism was also consistent with the fact that in reaction of hexafluoroacetylacetone (**Ia**) with urea and benzaldehyde under anhydrous conditions in an aprotic solvent (tetrahydrofuran) in the presence of catalytic amounts of *p*-toluenesulfonic acid we separated product **VIh** (Scheme 4, Tables 1, 2) with hexahydropyrimidine structure of **C** type.

The reaction of hexafluoroacetylacetone with thiourea and benzaldehyde under classical conditions of Biginelli condensation (ethanol, HCl) unlike that with urea results in a traditional product **VIi** (Scheme 4, Tables 1, 2). Apparently here the cyclocondensation by Biginelli occurs faster that the concurrent reaction of thiourea addition to both carbonyl groups of the 1,3-diketone. This fact may be due to the higher basicity of thiourea (pK_b 11.97) as compared to that of urea (pK_b 13.82) [14].

Since in the structure **C** of hexahydropyrimidine are present three asymmetrical carbon atoms compounds **Va–h**, **VIa–i** may exist as four possible diastereomers (and additionally four enantiomeric forms thereof). However the NMR spectra show that in each case exists a single diastereomer (apparently racemic one). The large conformational energies of the phenyl and alkoxycarbonyl (acyl) groups ($\Delta G_{C_6F_5}$ 12.1 kJ mol^{-1} and $\Delta G_{CO_2}43_{Et}$ 5.2 kJ mol^{-1} respectively) favor fixed conformations where these groups take equatorial orientation [9]. This is evidenced also by the calculated value of the coupling constants (11.0–11.8 Hz) corresponding to the axial coupling of the protons from these substituents. The comparison of the conformational energies of substituents suggests that the fluoroalkyl substituent is in equatorial position (for CF_3–ΔG 8.8 kJ mol^{-1}), and hydroxy group (ΔG 2.2 kJ mol^{-1}) in axial position (Fig. 3).

Interestingly in the IR spectrum of compound **VIc** recorded from a mull in the mineral oil two sets of bands from functional groups are observed apparently corresponding to two diastereomers (see Table 2). However in the NMR spectra of the product

Scheme 4.



Ia **VIh, i**

X = O (**VIh**), S (**VIi**).

registered in DMSO-d_6 is present a single set of resonances (Table 2). In the IR spectrum of compound **VIc** recorded from 0.1 M solution in chloroform also appears a single set of absorption bands belonging to amide fragment (3220, 1660 cm^{-1}), hydroxy (3400 cm^{-1}) and acetyl (1680 cm^{-1}) groups. Presumably unlike the other hexahydropyrimidines compound **VIc** exists as a mixture of two diastereomers in the solid state and as one isomer in solution. The experimental data obtained show that replacement in the Biginelli condensation of the nonfluorinated 3-oxoester component by 1,3-dicarbonyl compounds with partially or fully fluorinated substituent results in exclusive formation of derivatives of hexahydropyrimidines **Va–h, VIa–i**. The formation of stable hydrated heterocycles is characteristic of reactions between fluorinated 2-substituted 1,3-dicarbonyl compounds with dinucleophilic reagents [15], and it is caused by the presence of a strong electron-acceptor substituent.

On boiling compounds **Vd, g** and **VIa, e** in toluene in the presence of *p*-toluenesulfonic acid at azeotrope distillation of the forming water occurs the dehydration thereof to afford tetrahydropyrimidines **VIIIa, b, IXa, b** (Scheme 2, Tables 1, 2).

We demonstrated the possibility to build up bicyclic heterocyclic systems proceeding from the fluorinated tetrahydropyrimidines. For instance, tetrahydropyrimidine **VIIIb** on boiling in DMF with dibromoethane furnished a substituted thiazolopyrimidine hydrobromide **X** (Scheme 5, Tables 1, 2).

Thus we proposed routes to derivatives of pyrimidine molecular structures from fluoroalkyl-containing 1,3-dicarbonyl compounds. The products

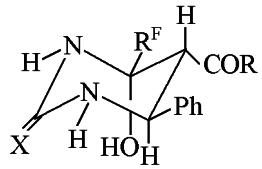
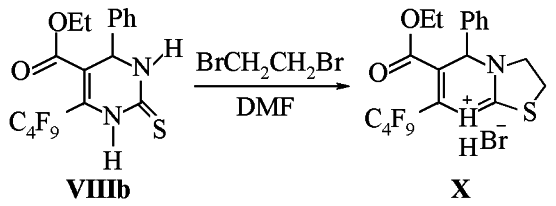


Fig. 3. Conformational structure of hexahydropyrimidines **Va–h, VIa–i**.

Scheme 5.



VIIIb **X**

obtained besides their own importance can serve as building blocks for various fused heterocyclic systems.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer Specord 75 IR in 400–4000 cm^{-1} range from mulls in mineral oil. ^1H NMR spectra were registered on spectrometer Tesla BS-567 A (80 MHz, reference TMS), ^{19}F and ^{13}C NMR spectra were measured on spectrometer Tesla BS-567 A at 75 and 20 MHz respectively with C_6F_6 and TMS as references. Elemental analysis was carried out on Carlo Erba CHNS-O EA 1108 analyzer.

Quantum-chemical calculations for fluoroalkyl-containing 1,3-dicarbonyl compounds **I, II** were performed by MNDO procedure with the use of MOPAC 6 software [13].

The yields and physical constants of compounds synthesized are listed in Tables 1, 2.

4,6-Bis(hydroxy)-4,6-bis(trifluoromethyl)hexahydropyrimidin-2-one (IIIa). (a) A mixture of 1,3-diketone **Ia** (416 mg, 2 mmol) and urea (120 mg, 2 mmol) was boiled in ethanol (8 ml) containing 2 drops of concn. HCl for 2 h. Ethanol was evaporated, the residue was washed with chloroform and a little water. As a result compound **IIIa** was obtained in 386 mg amount as a colorless powder.

(b) A mixture of benzaldehyde (212 mg, 2 mmol), 1,3-diketone Ia (416 mg, 2 mmol), urea (180 mg, 3 mmol), and ethanol (8 ml) containing 2 drops of concn. HCl was heated to reflux for 6 h. The product was precipitated from ethanol with water, filtered off, recrystallized from 50% ethanol, and dried in a vacuum. We obtained 236 mg of compound **IIIa**.

(c) A mixture of tetraol **VII** (488 mg, 2 mmol), benzaldehyde (212 mg, 2 mmol), and urea (120 mg, 2 mmol) was boiled in ethanol (8 ml) containing 2 drops of concn. HCl for 2 h. Ethanol was evaporated, the residue was recrystallized from 50% ethanol, and dried. We obtained 193 mg of product **IIIa**.

4,6-Bis(hydroxy)-4,6-bis(trifluoromethyl)hexahydropyrimidin-2-thione (IIIb). Along procedure *a* from 1,3-diketone **Ia** (416 mg, 2 mmol) and thiourea (152 mg, 2 mmol) after recrystallization from dichloromethane was obtained 318 mg of reaction product **IIIb** as a colorless powder.

2-Oxo-4,6-bis(trifluoromethyl)-1,2-dihydropyrimidine (IVa). To a solution of hexahydropyrimidine **IIIa** (536 mg, 2 mmol) in toluene (15 ml) was added *p*-toluenesulfonic acid (344 mg, 2 mmol). The mixture was boiled for 2 h, the forming water was distilled off in azeotrope. The toluene was evaporated, and the residue was sublimed. We obtained 316 mg of compound **IVa** as colorless crystals.

2-Mercapto-4,6-bis(trifluoromethyl)-1,2-dihydropyrimidine (IVb). In a similar way from hexahydropyrimidine **IIIb** (568 mg, 2 mmol) and *p*-toluenesulfonic acid (344 mg, 2 mmol) was obtained 308 mg of colorless crystalline product **IVb**.

2-Oxo-4-phenyl-6-(1,1,2,2-tetrafluoroethyl)-1,2-dihydropyrimidine (IVc). A mixture of 1,3-diketone **Ib** (496 mg, 2 mmol) and urea (120 mg, 2 mmol) was boiled in ethanol (8 ml) containing 2 drops of concn. HCl for 20 h. Ethanol was evaporated, the residue was dissolved in dichloromethane, the unreacted urea was filtered off, and the product was precipitated from dichloromethane with ethyl ether. As a result we obtained 185 mg of compound **IVc** as a colorless powder.

2-Mercapto-6-methyl-4-(1,1,2,2-tetrafluoroethyl)pyrimidine (IVd). Along procedure a from 1,3-diketone **Ic** (372 mg, 2 mmol) and thiourea (152 mg, 2 mmol) without hydrochloric acid additive was obtained compound **IVd** that on recrystallization from ethanol amounted to 145 mg (colorless powder).

Ethyl 4-hydroxy-4-difluoromethyl-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate (Va). Along procedure b a mixture of benzaldehyde (212 mg, 2 mmol), 3-oxoester **IIa** (332 mg, 2 mmol), urea (180 mg, 3 mmol), and ethanol (8 ml) containing two drops of concn. HCl was heated at reflux for 6 h and left overnight at 4°C. The separated precipitate was filtered off, recrystallized from ethanol, and dried in a vacuum. We obtained 471 mg of compound **Va** as a colorless powder.

Methyl 4-hydroxy-2-oxo-4-(1,1,2,2-tetrafluoroethyl)-6-phenylhexahydropyrimidine-5-carboxylate (Vb). In a similar way from benzaldehyde (212 mg, 2 mmol), 3-oxoester **IIb** (404 mg, 2 mmol), and urea

(180 mg, 3 mmol) was obtained 553 mg of reaction product **Vb** as a colorless powder.

Methyl 4-heptafluoropropyl-4-hydroxy-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate (Vc). In a similar way from benzaldehyde (212 mg, 2 mmol), 3-oxoester **IIc** (540 mg, 2 mmol), and urea (180 mg, 3 mmol) was obtained 610 mg of reaction product **Vc** as a colorless powder.

Ethyl 4-hydroxy-4-nonafluorobutyl-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate (Vd). In a similar way from benzaldehyde (212 mg, 2 mmol), 3-oxoester **IId** (668 mg, 2 mmol), and urea (180 mg, 3 mmol) was obtained 771 mg of reaction product **Vd** as a colorless powder.

Methyl 4-hydroxy-4-(1,1,2,2-tetrafluoroethyl)-2-thioxo-6-phenylhexahydropyrimidine-5-carboxylate (Ve). In a similar way from benzaldehyde (212 mg, 2 mmol), 3-oxoester **IIb** (404 mg, 2 mmol), and thiourea (228 mg, 3 mmol) was obtained 336 mg of reaction product **Ve** as a colorless powder.

Methyl 4-heptafluoropropyl-4-hydroxy-2-thioxo-6-phenylhexahydropyrimidine-5-carboxylate (Vf). In a similar way from benzaldehyde (212 mg, 2 mmol), 3-oxoester **IIc** (540 mg, 2 mmol), and thiourea (228 mg, 3 mmol) was obtained 408 mg of reaction product **Vf** as a colorless powder.

Ethyl 4-hydroxy-4-nonafluorobutyl-2-thioxo-6-phenylhexahydropyrimidine-5-carboxylate (Vg). In a similar way from benzaldehyde (212 mg, 2 mmol), 3-oxoester **IId** (668 mg, 2 mmol), and thiourea (228 mg, 3 mmol) was obtained 448 mg of reaction product **Vg** as a colorless powder.

Ethyl 4-hydroxy-2-thioxo-4-trifluoromethyl-6-phenylhexahydropyrimidine-5-carboxylate (Vh). In a similar way from benzaldehyde (212 mg, 2 mmol), 3-oxoester **IIe** (368 mg, 2 mmol), and thiourea (228 mg, 3 mmol) was obtained 300 mg of reaction product **Vh** as a colorless powder.

5-Benzoyl-4-hydroxy-4-(1,1,2,2-tetrafluoroethyl)-6-phenylhexahydropyrimidin-2-one (VIa). In a similar way from benzaldehyde (212 mg, 2 mmol), 1,3-diketone **Ib** (496 mg, 2 mmol), and urea (180 mg, 3 mmol) was obtained 301 mg of compound **VIa** as a colorless powder.

5-Acetyl-4-hydroxy-4-(1,1,2,2-tetrafluoroethyl)-6-phenylhexahydropyrimidin-2-one (VIb). In a similar way from benzaldehyde (212 mg, 2 mmol), 1,3-diketone **Ic** (372 mg, 2 mmol), and urea (180 mg, 3 mmol) was obtained 221 mg of compound **VIb** as a colorless powder.

5-Acetyl-4-hydroxy-4-trifluoromethyl-6-phenylhexahydropyrimidin-2-one (VIc). In a similar way from benzaldehyde (212 mg, 2 mmol), 1,3-diketone **Id** (308 mg, 2 mmol), and urea (180 mg, 3 mmol) was obtained 193 mg of compound **VIc** as a colorless powder.

5-Benzoyl-4-hydroxy-4-trifluoromethyl-6-phenylhexahydropyrimidin-2-one (VId). In a similar way from benzaldehyde (212 mg, 2 mmol), 1,3-diketone **Ie** (432 mg, 2 mmol), and urea (180 mg, 3 mmol) was obtained 306 mg of compound **VId** as a colorless powder.

5-Acetyl-4-hydroxy-4-trifluoromethyl-6-phenylhexahydropyrimidine-2-thione (VIe). In a similar way from benzaldehyde (212 mg, 2 mmol), 1,3-diketone **Ia** (308 mg, 2 mmol), and thiourea (228 mg, 3 mmol) was obtained 140 mg of compound **VIe** as a colorless powder.

5-Benzoyl-4-hydroxy-4-trifluoromethyl-6-phenylhexahydropyrimidine-2-thione (VIf). In a similar way from benzaldehyde (212 mg, 2 mmol), 1,3-diketone **Id** (432 mg, 2 mmol), and thiourea (228 mg, 3 mmol) was obtained 228 mg of compound **VIf** as a colorless powder.

5-Benzoyl-4-hydroxy-4-(1,1,2,2-tetrafluoroethyl)-6-phenylhexahydropyrimidin-2-thione (VIg). In a similar way from benzaldehyde (212 mg, 2 mmol), 1,3-diketone **Ie** (496 mg, 2 mmol), and thiourea (228 mg, 3 mmol) was obtained 297 mg of compound **VIg** as a colorless powder.

4-Hydroxy-5-trifluoroacetyl-4-trifluoromethyl-6-phenylhexahydropyrimidin-2-one (VIh). A mixture of benzaldehyde (212 mg, 2 mmol), 1,3-diketone **Ia** (416 mg, 2 mmol), urea (180 mg, 3 mmol), *p*-toluenesulfonic acid (258 mg, 1.5 mmol), and tetrahydrofuran (8 ml) was heated at reflux for 2 h. The product was precipitated from tetrahydrofuran with water, washed with dichloromethane, and dried in a vacuum. We obtained 214 mg of compound **VIh** as a colorless powder.

4-Hydroxy-5-trifluoroacetyl-4-trifluoromethyl-6-phenylhexahydropyrimidin-2-thione (VIh). Along procedure *b* from benzaldehyde (212 mg, 2 mmol), 1,3-diketone Ia (416 mg, 2 mmol), and thiourea (228 mg, 3 mmol) was prepared a product that after separation was washed with water and dichloromethane. We obtained 114 mg of compound **VIi** as colorless powder.

Ethyl 6-nonafluorobutyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VIIIa). To a solution of hexahydropyrimidine **Vd** (965 mg,

2 mmol) in toluene (15 ml) was added 100 mg of *p*-toluenesulfonic acid, and the mixture was boiled for 6 h with azeotrope distillation of the forming water. The solution was cooled to room temperature, and the small portion of solids was filtered off. Then the filtrate was partially evaporated, and the precipitate formed was filtered off. As a result we obtained 520 mg of compound **VIIIa** as a colorless powder.

Ethyl 6-nonafluorobutyl-2-thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VIIIb). In a similar way from hexahydropyrimidine **Vg** (996 mg, 2 mmol) was obtained 462 mg of compound **VIIIb** as colorless powder.

5-Benzoyl-2-oxo-6-(1,1,2,2-tetrafluoroethyl)-4-phenyl-1,2,3,4-tetrahydropyrimidine (IXa). In a similar way from hexahydropyrimidine **VIa** (793 mg, 2 mmol) was obtained 333 mg of compound **IXa** as a colorless powder.

5-Benzoyl-6-(1,1,2,2-tetrafluoroethyl)-2-thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine (IXb). In a similar way from hexahydropyrimidine **VIe** (825 mg, 2 mmol) was obtained 316 mg of compound **IXb** as a colorless powder.

Ethyl 7-nonafluorobutyl-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate hydrobromide (X). To a boiling solution of tetrahydropyrimidine **VIIIb** (961 mg, 2 mmol) in DMF (5 ml) was added dibromoethane (395 mg, 2.1 mmol), and the mixture was boiled for 25 min. The precipitate that separated on cooling was filtered off and recrystallized from ethanol. We obtained 493 mg of product **X** as a colorless powder.

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