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FLUOROALKYL-CONTAINING β,β'-TRICARBONYL COMPOUNDS: TAUTOMERISM AND REACTION WITH N-NUCLEOPHILES

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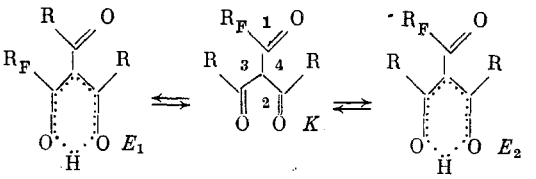
The tautomeric composition of α-polyfluoroacyl derivatives of acetylacetone and malonic ester has been established and it has been shown that with N-nucleophiles (ammonia, 1,2-ethylenediamine, o-phenylenediamine) these compounds undergo 'acid' decomposition with the elimination of the polyfluoroacyl group. With hydrazines, malonic ester derivatives react similarly but acetylacetone derivatives undergo cyclization into pyrazoles. The regiodirectivity of the interaction of fluoroalkyl-containing β,β'-tricarbonyl compounds with N-nucleophiles does not depend on their tautomeric composition and is determined by orbital control.

We have previously studied the structure and regiodirectivity of the interaction between α-polyfluoroacyl derivatives of acetic acid esters (I) and N-nucleophiles [1-3].

In the present work we have studied tautomers and reactions of α-polyfluoroacyl derivatives of acetylacetone (II) and malonic ester (III) (the synthesis of which was described in a previous communication [4]) with N-nucleophiles, and we have also carried out a qualitative examination of the regiodirectivity of the interaction between the fluoroalkyl-containing β,β'-tricarbonyl compounds (β,β-FTC) (I)-(III) mentioned above in a framework of perturbation of molecular orbitals.

Compounds (II), (IIIa, b) were obtained by acylation of acetylacetone and malonic ester by means of the acid fluorides of perfluorocarboxylic acids (PFA) – perfluoropropionic and perfluorovaleric – or α-hydroxyperfluoropropylene [4], and (IIIc) by acylation of malonic ester by the acid chloride of 3-hydroperfluoropropionic acid according to the method given in [1].

In the PMR spectra of compounds (IIa, b) there were singlets from the magnetically equivalent protons of the acetyl groups (2.18-2.20 ppm, 6H) and downfield, the enol proton (17.41-17.42 ppm, 1H), which is evidence of their existence exclusively in the form of the E_2 tautomer (Table 1)



(IIa, b) (IIIa—c)

R = Me (II); R = OEt (III); $R_F = C_2F_5$ (a); C_4F_9 (b); $H(CF_2)_2$ (c).

At the same time, in the PMR spectra of compounds (IIIa-c), in addition to the double set of signals from the methyl and methylene protons of the ester group (1.20-1.45 ppm, m, 6H; 4.0-4.5 ppm, m, 4H), signals are detected from the α-protons of the triketo form (4.88-

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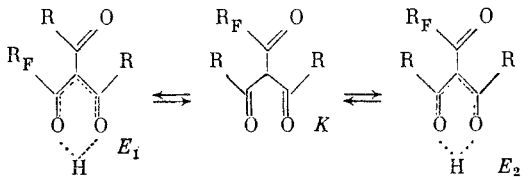
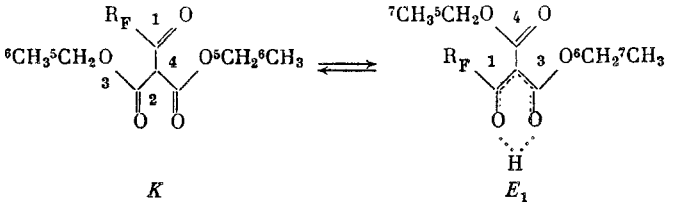
TABLE 1. PMR Spectra and Tautomer Content for Compounds (IIa, b) and (IIIa-c) (CCl_4, 34°C)



Compound	R	R_F	δ, ppm						Enol	Tautomer content, %	
			triketo form			enol					
			Me	CH	$H(CF_2)_2$	Me	OH	$H(CF_2)_2$		tri-keto form	enol
(IIa)	Me	C_2F_5	–	–	–	2.18	17.41	–	E_2	–	100
(IIb)	Me	C_4F_9	–	–	–	2.20	17.42	–	E_2	–	100
(IIIa) *	OEt	C_2F_5	–	4.91	–	–	12.83	–	E_1	46	54
(IIIb) *	OEt	C_4F_9	–	4.91	–	–	12.87	–	E_1	44	56
(IIIc) *	OEt	$H(CF_2)_2$	–	4.88	6.21	–	12.92	6.16	E_1	45	55

*Signals of the methyl and methylene protons of the ethoxycarbonyl groups lie in the 1.20-1.45 and 4.0-4.5 ppm regions, respectively.

TABLE 2. ^{13}C NMR Spectra of Compounds (IIIa-c)* ($CDCl_3$, 34°C)



Compound	Triketo form			Enol form				
	C^1	C^2, C^4	C^5	C^1	C^2	C^3	C^4	C^7
(IIIa)	184.65	162.69	14.01	159.03	106.44	170.39	162.91	14.01
(IIIb)	184.61	162.88	14.04	159.33	106.70	170.61	163.21	14.04
(IIIc)	185.92	161.12	12.03	159.70	103.49	168.59	161.42	12.03

*C^2 and C^5 signals of triketo form and C^5 and C^6 of enol form are situated in the 63.77-61.33 ppm region.

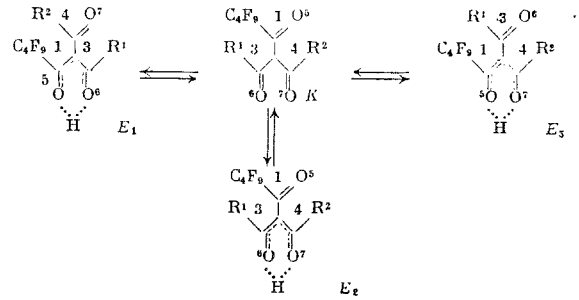
4.91 ppm, s) and the enol proton (12.83-12.92 ppm, br. s), corresponding to tautomer E_1. The tautomer content of the mixture was established in terms of the ratio of the integral intensities of the signals from the α-proton and the enol (Table 1). The results which we obtained for compounds (IIIa-c) are in general agreement with those found in the literature for trifluoroacetyl malonic ester [5] although the enol content in the latter case is somewhat higher.

A comparison of the ^{13}C NMR spectra of compounds (IIa, b), (IIIa-c), and the fluoroalkyl-containing β-diketone $C_4F_9COCH_2COMe$ (IV) (100% enol) and β-ketoester $C_4F_9COCH_2COOEt$ (V) (90% enol) [3] unequivocally supports our assignment of the tautomeric forms. Thus, the chemical shifts of the C^1 carbonyl atom with fluoroalkyl substitution of the E_1 enol forms of compounds (IIIa-c) and the β-ketoester (V) (159.03-159.70 and 161.57 ppm, respectively) correlate well between themselves, and so also in the case of their keto forms (184.61-185.92 and 187.36 ppm) (Table 2). At the same time, the position of the signal of the C^1 carbonyl atom of β,β'-FTC (IIa, b) (189.28-189.36 ppm) is essentially different from that of the β-diketone (IV) (177.95 ppm) and is close to the result for 1,1,1-trifluoroacetone (187.7 ppm [6]) which lends support to their existence in the E_2 tautomeric form with a nonchelated perfluoroacyl group. For comparison of the properties of the β,β'-FTC (II), (III) which we prepared with the α-polyfluoroacyl derivatives of acetoacetic ester (I) which we examined previously [2], we studied their reaction with NH_3, 1,2-ethylenediamine, o-phenylenediamine, and hydrazines. In the hydrocarbon series are described reactions of acylmalonic esters with o-phenylenedi-

TABLE 3. Products of the Reaction of β,β'-FTC with Amines

Compound	Mp, °C (solvent)	Found/Calculated, %				Empirical formula	IR spectrum, ν, cm^{-1}			PMR spectrum δ, ppm		
		C	H	F	N		C=O	C=N C=C	N—H	Me	H(C_6H_5)	N—H
(VIb)	110–111 ($CHCl_3$)	23,17 / 22,83	1,37 / 0,77	64,49 / 65,00	5,45 / 5,32	$C_5H_2F_9NO$	1700	–	3200, 3370	–	–	–
(VIIa)	144–145 ($CHCl_3$ – hexane 1 : 1)	27,64 / 27,29	2,15 / 1,72	53,87 / 53,95	8,31 / 7,96	$C_8H_6F_{10}N_2O_2$	1680	–	3310	–	–	–
(VIIIb)	174–175 ($CHCl_3$ – hexane 3 : 2)	39,20 / 39,30	1,61 / 1,50	50,39 / 50,86	8,46 / 8,33	$C_{11}H_5F_9N_2$	–	1530, 1590	3067	–	7,35–7,80	4,04 s
(XIa)	91–93 (hexane)	39,79 / 39,68	2,95 / 2,91	39,23 / 39,23	11,47 / 11,57	$C_8H_7F_5N_2O$	1650	1560	3620, 3730	2,48 s, 2,50 s	–	9,52 s
(XIb)	78–80 (hexane)	35,17 / 35,10	2,40 / 2,06	49,92 / 49,97	8,11 / 8,19	$C_{10}H_7F_9N_2O$	1650	1565	3600, 3730	2,49 s, 2,54 s	–	9,13 s
(XIIa)	62–63 (hexane)	53,23 / 52,84	3,42 / 3,48	30,11 / 29,85	8,83 / 8,80	$C_{14}H_{11}F_5N_2O$	1660	1590	–	2,47 s, 2,58 s	7,26–7,56 m	–

TABLE 4. Charge Distribution in the Tautomeric Forms of Fluoroalkyl-Containing β,β'-Tricarbonyl Compounds (Ib)-(IIIb)

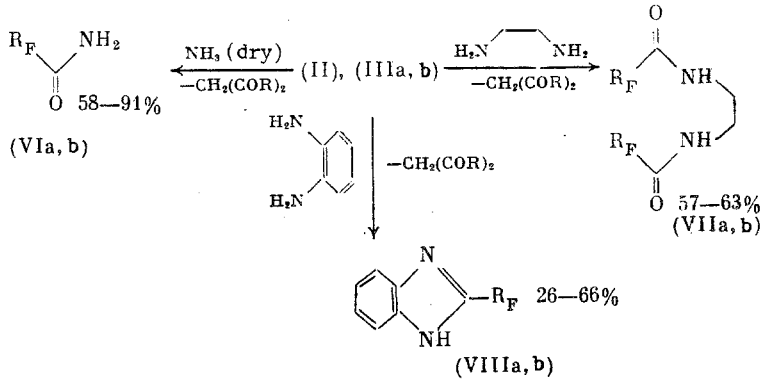


R¹=Me, R²=OEt (I); R¹=R²=Me (II); R¹=R²=OEt (III).

Compound	Tautomer	Full atomic charges in electron charge units – MINDO/3 approximation					
		C¹	C³	C⁴	O⁵	O⁶	O⁷
(IIb)	E_2	0.490	0.612	0.594	−0.460	−0.535	−0.560
(Ib)	E_1	0.461	0.625	0.873	−0.464	−0.558	−0.594
(Ib)	E_2	0.497	0.545	0.889	−0.465	−0.512	−0.558
(IIIb)	$E_1=E_3$	0.448	0.895	0.882	−0.468	−0.630	−0.585
(IIIb)	K	0.490	0.834	0.832	−0.436	−0.561	−0.557

amine, phenylhydrazine, and 1,1-dimethylhydrazine leading to acid cleavage with the formation of phenylhydrazines of carboxylic acids [7], 2-methylbenzimidazole [8] or else to heterocyclization into substituted Δ^3-pyrazolinimides [9]. 2,4-Dinitrophenylhydrazine forms the corresponding hydrazone with acetylmalonic ester [10].

We have established that compounds (II, IIIa, b) are similar to compound (I) [2] in their reaction with NH_3, 1,2-ethylenediamine, and o-phenylenediamine in proton-donor (95% ethanol) and aprotic (anhydrous diethyl ether) media, undergoing acid decomposition into amides of perfluoroacids (VI), N,N'-bis(polyfluoroacyl)ethylenediamine (VII), or 2-perfluoroalkylbenzimidazoles (VIII) (Table 3).



In the case of compounds (IIIa, b) it was possible to isolate the malonic ester from the reaction mixture. The yield of products was essentially independent of the structure of the fluoroalkyl radical and the reaction medium.

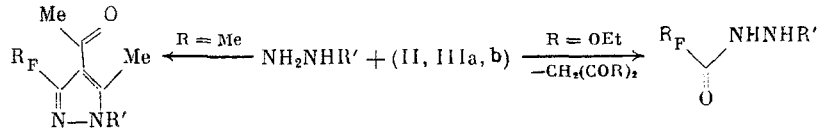
β,β'-FTC (II) and (III) reacted with hydrazines in different ways. Whereas compounds (IIIa, b) gave only the products of acid decomposition – hydrazides of perfluoroacids (IX), (Xa, b) – independently of the reaction medium and the structure of the fluoroalkyl substituent, the acetylacetone derivatives (IIa, b) were cyclized into substituted pyrazoles (XIa, b), (XIIa) (Table 3) (see top of following page).

The above examples, together with the results of [2], show that attack by N-nucleophiles on β,β'-FTC (I)-(III) is oriented at the polyfluoroacyl group independently of its participation in enolization and of the tautomeric composition of the compounds. Depending on the structure of the β,β'-FTC (I)-(III), stabilization of the addition intermediate which is formed takes place either by acid decomposition or by heterocyclization.

TABLE 5. Reactivity Index Distribution (Fukui) of Molecular Orbitals of Tautomers of Fluoroalkyl-Containing β,β'-Tricarbonyl Compounds (Ib)-(IIIb)*

Compound	Tautomer	Fukui index of orbitals HOMO/LUMO — MINDO/3 approximation					
		C^1	C^3	C^4	O^5	O^6	O^7
(IIb)	E_2	0,002 / 0,022	0,105 / 0,001	0,123 / 0	0,028 / 0,013	0,462 / 0,001	0,584 / 0
(Ib)	E_1	0,134 / 0,023	0,120 / 0	0,001 / 0,001	0,220 / 0,007	0,412 / 0,002	0,012 / 0,001
(Ib)	E_2	0,109 / 0,021	0,031 / 0,001	0,069 / 0	0,328 / 0,011	0,119 / 0,001	0,419 / 0
(IIIb)	$E_1=E_3$	0,115 / 0,022	0,032 / 0,001	0,005 / 0,001	0,200 / 0,007	0,310 / 0,001	0,044 / 0,001
(IIIb)	K	0,150 / 0,019	0,003 / 0,001	0,002 / 0,003	0,339 / 0,009	0,130 / 0,001	0,130 / 0,001

*Numbering of atoms in tautomers as in Table 4.



(XIa,b), 46—54%
(XIIa), 57—61%

(IXa,b), 51—73%
(Xa,b), 81—97%

R' = H (IX), (XI); R' = Ph (X), (XII)

To try to explain the directivity of the interaction between β,β'-FTC and nucleophiles, we carried out quantum chemical calculations of their tautomeric forms on compounds (I)-(IIIb) as examples, using the MO LCAO standard method with CNDO/2 and MINDO/3 approximations (Tables 4 and 5). The accuracy of the calculations was supported by the closeness of the dipole moments so obtained to the experimental values (Table 6). As can be seen from the charge distribution on the atoms (Table 4) attack by nucleophiles on β,β'-FTC in a charge-controlled reaction must take place at the acetyl (IIb, enol E_2) or ester (IIIb, enol E_1, keto form; Ib, enols E_1 and E_2) groups. At the same time, the results obtained for the reactivity indexes (Fukui) for the lowest unoccupied molecular orbitals (LUMO) provided evidence that attack by nucleophiles on β,β'-FTC (I)-(III) under orbital control conditions must take place at the C^1 carbonyl atom of the polyfluoroacyl group independently of its participation in enolization; this is in good agreement with the results which we obtained. Thus, the reaction of β,β'-FTC with N-nucleophiles can be understood as being orbitally controlled.

EXPERIMENTAL

IR spectra were obtained on a Specord IR-75 spectrometer as mulls in mineral oil. Proton and carbon-13 NMR spectra were run on a Tesla BS-567A instrument (100 and 25.1 MHz) in $CDCl_3$ and CCl_4 with TMS as internal standard. Dielectric constants for calculation of dipole moments were determined on a Tangens 2M instrument in benzene at 25 ± 0.1°C at a frequency of 1 MHz.

Compounds described in the literature — (IIa, b), (IIIa, b) [4], (VIa) [12], (VIIb) [2], (VIIIa) [13], (IXa, b) (Xa, b) [14-17] — were identified from known samples. Calculations were carried out using the program given in [11]. Structural data, taken from [18-20], were partially optimized.

Carbon-13 NMR spectra ($CDCl_3$, 34°C, δ, ppm) for compound (IIa): 24.69 (C^5, C^6), 112.99 (C^2), 189.36 t (C^1, J = 27 Hz), 194.73 (C^3, C^4); for compound (IIb): 24.76 (C^5, C^6), 113.31 (C^2), 189.28 t (C^1, J = 27 Hz), 197.99 (C^3, C^4).

Ethyl-2-ethoxycarbonyl-3-oxo-4,4,5,5-tetrafluoropentanoate (IIIc). By the method of [1], from 20.8 g (0.13 mole) malonic ester, 16.4 g (0.14 mole) magnesium diethoxide, and 23.5 g (0.14 mole) 2,2,3,3-tetrafluoropropionyl chloride, 15.0 g (40%) compound (IIIc) was obtained, bp 106-107°C (3 mm). IR spectrum (ν, cm^{-1}, film): 3455 (OH), 1765, 1735, 1665

TABLE 6. Dipole Moments of β,β'-FTC (I)-(IIIb)

Compound	Tautomer	Tautomer content, %	μ_{calc} for tautomer	μ_{calc} overall	μ^{*}_{exp}
(Ib)	E_1	19	3.95	2,54	2.58
(Ib)	E_2	81	2,24		
(IIb)	E_2	100	1,18	1,18	1,56
(IIIb)	E_1	56	4,46	4,30	3,94
(IIIb)	K	44	4,09		

*Accuracy of measurement ±0.02.

(C=O), 1460 (C=C). Found, %: C 41.46, H 4.18, F 26.28. $C_{10}H_{12}F_4O_5$. Calculated, %: C 41.68, H 4.20, F 26.37.

Reaction with NH_3. Dry NH_3 was passed into a solution of 8.0 g (19.7 mmoles) compound (IIIb) in 50 ml dry ether (or 95% ethanol) at −40°C over a period of 0.5 h. Cooling was stopped, the solvent evaporated over 3 h and 100 ml hexane added to the residue. The insoluble material was filtered off and crystallized from 150 ml $CHCl_3$. Yield 3.3 g (64%) [in ethanol, 3.03 g (59%)] amide (VIb) (Table 3).

Evaporation of the filtrate and distillation of the residue in vacuum yielded 2.94 g (93%) [in ethanol, 2.65 g (84%)] malonic ester.

Reactions with (IIa, b) and (IIIa) were carried out in a similar way. The amide (VIa) obtained from (IIa) and (IIIa) was identical in physical constants with that of [12].

Reaction with o-Phenylenediamine. o-Phenylenediamine (1.65 g, 15.3 mmoles) was added in portions to a stirred (20°C) solution of 4.69 g (15.3 mmoles) compound (IIIa) in 50 ml ether over a period of 0.5 h. After 1 h the solvent was removed and the residue crystallized from 180 ml 1:4 hexane/chloroform. The benzimidazole (VIIIa) (1.91 g, 53%) obtained was identical with that described in [13]. The mother liquor was evaporated and the residue distilled in vacuum to yield 2.17 g (88%) malonic ester.

The same procedure was used for compounds (IIa, b) and (IIIb).

Reaction with 1,2-Ethylenediamine. A solution of 3.69 g (15 mmoles) compound (IIa) in 50 ml ether was cooled to −40°C, stirred, and 0.9 g (15 mmoles) 1,2-ethylenediamine added. The reaction mixture was stirred for 3 h gradually increasing the temperature to 20°C. The residue after evaporating off the solvent was recrystallized from 50 ml 1:1 hexane/chloroform to yield 1.65 g (63%) amide (VIIa) (Table 3).

Reaction with (IIb) and (IIIa, b) was carried out in a similar manner. The amide (VIIb) was identical with that of [2].

Reaction of (IIIa, b) with Hydrazine and Phenylhydrazine. A solution of 9.14 g (29.9 mmoles) compound (IIIa) in 50 ml 95% ethanol (ether) was cooled to −40°C, stirred, and 0.96 g (29.9 mmoles) anhyd. hydrazine added. Stirring was continued for 3.5 h, allowing the temperature to rise gradually to 20°C, the solvent removed, and 100 ml hexane added. The residue was separated and crystallized from aqueous ethanol to yield 3.51 g (66%) (in ether, 3.88 g, 73%) hydrazide (IXa). From the filtrate, 3.61 g (75%) (in ether, 4.18 g, 87%) malonic ester was isolated by vacuum distillation. Compound (IXb) was prepared from (IIIb) in a similar way: yield 51-73%.

The constants of the prepared perfluoroacid hydrazides (IXa, b) were identical with those of [14-17].

The above method was used for the reaction of (IIIa, b) with phenylhydrazine to prepare perfluoroacid phenylhydrazides (Xa, b) in 81-97% yield; the constants were in agreement with those of [14-17].

Ethyl Ester of 3-Perfluoroalkyl-5-methyl-4-pyrazolecarboxylic Acids (XIa, b). A solution of 8.05 g (23.3 mmoles) compound (IIb) in 50 ml ether (95% ethanol) was stirred and cooled to −40°C and 0.75 g (23.4 mmoles) anhyd. hydrazine added. This was stirred for 3 h, gradually warming to 20°C. The residue after evaporation of the solvent was crystallized from 100 ml hexane to yield 4.34 g (54%) pyrazole (XIb) (in ethanol, 4.25 g, 53%). Pyrazole (XIa), yield 46-54%, was prepared in a similar way (Table 3).

Ethyl Ester of 3-Perfluoroethyl-5-methyl-1-phenyl-4-pyrazolecarboxylic Acid (XIIa). A solution of 7.18 g (29.2 mmoles) compound (IIa) in 50 ml ether (ethanol) was cooled to −40°C and 3.16 g (29.2 mmoles) phenylhydrazine added. Stirring was continued for 3 h, gradually warming to 20°C. The solvent was removed and the residue crystallized from 50 ml hexane to yield 5.33 g (57%) pyrazole (XIIa) (in ethanol, 5.75 g, 61%) (Table 3).

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