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SYNTHESIS OF NEW FLUORINE-CONTAINING DERIVATIVES OF QUINOXALINE 1,4-DIOXIDES AND CONDENSED SYSTEMS DERIVED FROM THEM*

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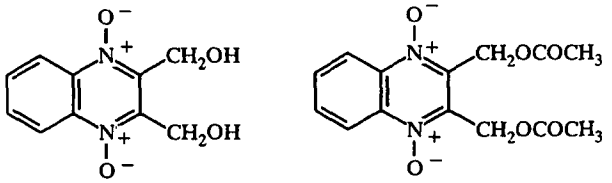
The Beirut reaction of 5,6-difluorobenzofuroxan with 1,3-diketones, β-ketoesters, and amides produces 6,7-difluoroquinoxaline 1,4-dioxides. The condensation of 2-ethoxycarbonyl-6,7-difluoro-3-methylquinoxaline 1,4-dioxide is studied. Fluorinated furo[3,4-b]- and pyrrolo[3,4-b]quinoxaline 4,9-dioxides are synthesized and further functionalized by nucleophilic substitution of fluorine and reduction of the N–O bond.

Quinoxaline 1,4-dioxide and its condensed derivatives have been show to display various types of biological activity (antibacterial, fungicidal, herbicidal, etc.) [1]. In particular, 2,3-di(hydroxymethyl)- and 2,3-di(acetoxymethyl)quinoxaline 1,4-dioxides are used in medicine as effective antibacterial drugs [2].



Little is known about the synthesis of furo[3,4-*b*]- and pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides [2-5]. However, they are also known as interesting biologically active compounds. The synthesis of fluorinated derivatives of furo[3,4-*b*]- and pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides has not been reported. Nevertheless, fluorinated derivatives of azaheterocycles are very interesting because many of them exhibit high biological activity compared with the unfluorinated analogs. For example, a new generation of wide-spectrum antibacterial drugs has been found among fluorinated derivatives of quinolone carboxylic acids [6]. Compounds with other types of biological activity, antitumor and antivirus, including against HIV infection, have recently been found in this class [7]. Furthermore, it was recently demonstrated that the fluorine atom in fluoroarenes can form C–F···H–N hydrogen bonds to heterocyclic bases of DNA, similar to the oxygen atom of uracil [8]. This undoubtedly stimulates interest in the synthesis of fluorinated benzodiazines.

In the present work we report the synthesis of previously unknown 7-mono- and 6,7-difluorinated derivatives of quinoxalines, quinoxaline 1,4-dioxides, and the furo[3,4-*b*]- and pyrrolo[3,4-*b*]annelated systems derived from them.

* Dedicated to Professor Henk van der Plas on his 70th birthday.

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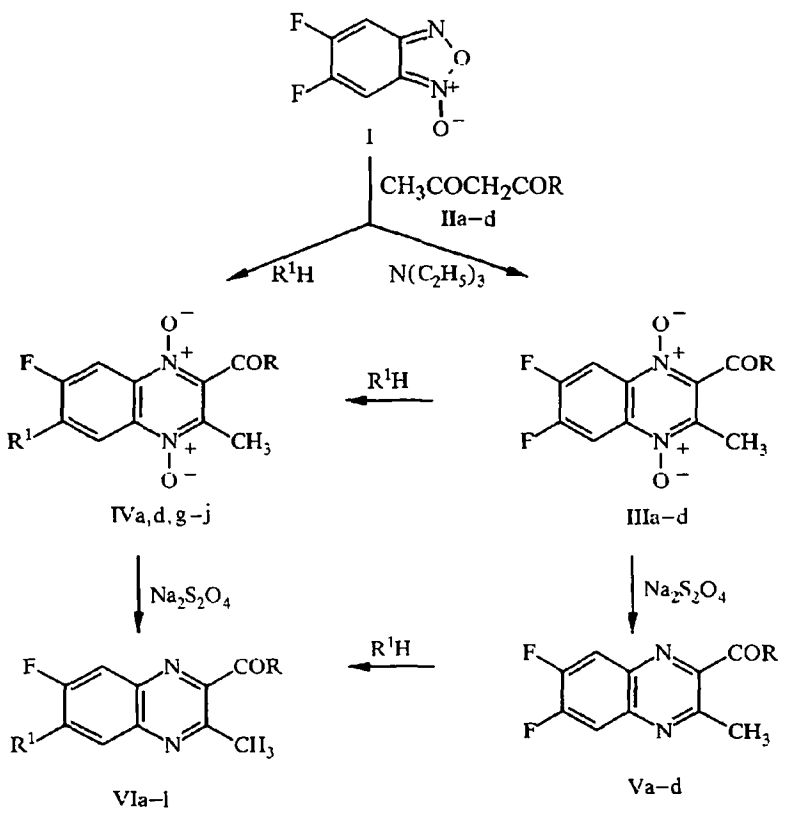
Despite the large number of publications on the synthesis of quinoxaline 1,4-dioxides [9-11], the behavior of the fluorine-containing benzofuroxans toward this reaction is little studied [12, 13]. In continuation of our studies [14, 15] of fluorinated heterocycles, we studied the reaction of 5,6-difluorobenzofuroxan (I) with the enolates of acetylacetone (IIa), acetoacetic ester (IIb), benzoylacetone (IIc), and acetoacetanilide (IId) (Scheme 1). Earlier [14] we demonstrated that 5,6-difluorobenzofuroxan readily reacts with enamines of cyclic ketones to give in good yields the annelated quinoxaline 1,4-dioxides. The similarity between the enamines and the enolates prompted us to study the reaction of the latter with 5,6-difluorobenzofuroxan (I).

Scheme 1



II,III, V, a R = Me, b R = OEt, c R = Ph, d R = PhNH;
IV, VIa-c R = Me, d-f R = OEt, g-i R = Ph, j-l R = PhNH;
IV, VIa, d, g, j R^1 = morpholino, b, e, h, k R^1 = 1-methylpiperazino,
c, f, i, l R^1 = pyrrolidino

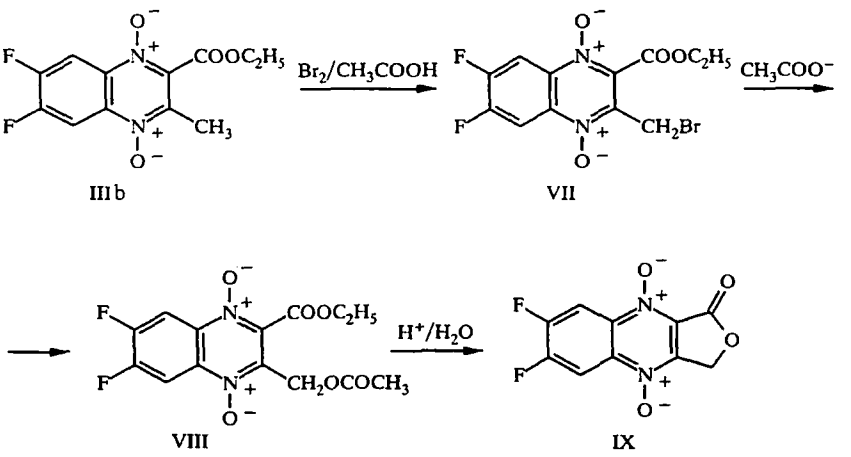
Furoxan I in ethanol or dioxane smoothly reacts with enolates at room temperature in the presence of a base, triethylamine. However, the best results (yields of 6,7-difluoroquinoxaline 1,4-dioxides IIIa-d 60-72%) are achieved if the reaction is carried out using triethylamine as solvent and catalyst simultaneously. The situation was different if the reaction was carried out in the presence of cyclic imines, morpholine, methylpiperazine, and pyrrolidine. The reaction was carried out in anhydrous ethyl alcohol, dioxane, or DMF in the presence of 1.2-2.5 moles of the corresponding imine. Under these conditions the transformation of I into quinoxaline 1,4-dioxides was accompanied by the selective substitution of the fluorine atom at $C_{(6)}$ by the saturated N-heterocycle. The ease replacement of the fluorine atom is explained by the activating effect of the carbonyl group at $C_{(2)}$. We previously observed this in other reactions of 6,7-difluoroquinoxaline 1,4-dioxides [14]. The 6-substituted quinoxaline 1,4-dioxides IVa, d, j were prepared in 44-60% yield by reaction of I with acetylacetone, acetoacetic ester, and

acetoacetanilide, respectively, in the presence of morpholine; dioxides IVg-i, by reaction of I with benzoylacetone in the presence of morpholine, methylpiperazine, and pyrrolidine (Scheme 1). In the other cases, variation of the reaction condition (duration, temperature) as well as ratio of reagents did not change the product yields due to formation of tars.

The prepared compounds were functionalized by reduction of the fluorinated quinoxaline 1,4-dioxides to the corresponding quinoxalines and the possiblility of nucleophilic substitution of the fluorine atom in the N-oxides and their reduced analogs was studied. The N-oxide groups in quinoxaline 1,4-dioxides III and IV were removed using sodium dithionite ($Na_2S_2O_4$). The yields of quinoxalines Va-d and VIa-d were optimal at a reductant–1,4-dioxide ratio of 4:1. Mixtures of isomers in various ratios that depended on the relative amount of reagents, temperatures, reaction times, and solvent were observed by chromatography in nucleophilic substitution reactions of the 6,7-difluoroquinoxaline 1,4-dioxides IIIa-d with the cyclic imines in which the fluorine atom at $C_{(6)}$ and $C_{(7)}$ was replaced. Nucleophilic substitution in the corresponding quinoxalines Va, b, d, which do not contain N-oxides, occurs regioselectively. This enabled the preparation in yields of 64-80% (Scheme 1) of pure products by replacing the fluorine atom at $C_{(6)}$ of VIb, c, e, f, k, l.

In the present work we synthesized the fluorinated derivatives of furo[3,4-*b*]- and pyrrolo[3,4-*b*]-quinoxaline 4,9-dioxides from 2-ethoxycarbonyl-3-methyl-6,7-difluoroquinoxaline 1,4-dioxide (IIIb) and its bromomethyl derivative (VII) as the key intermediates (Scheme 2 and 3). We found that 2-ethoxycarbonyl-6,7-difluoro-3-methylquinoxaline 1,4-dioxide (IIIb) is readily brominated in DMF–$CHCl_3$ or in a mixture of acetic acid and conc. H_2SO_4 to give the bromomethyl derivative VII (Scheme 2). The corresponding acetoxy derivative VIII containing both fluorine atoms is prepared by nucleophilic substitution of the bromine atom in VII. Acid hydrolysis of the ester VIII by conc. HCl is accompanied by spontaneous cyclization of the intermediate hydroxymethyl derivative into the lactone, 6,7-difluoro-1-oxo-1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-dioxide (IX) (Scheme 2).

Scheme 2



An excess of ammonia, ethylamine, cyclohexylamine, or monoethanolamine transforms bromomethyl derivative VII into the corresponding 2-substituted 6,7-difluoro-1-oxo-1,3-dihydropyrrolo[3,4-*b*]quinoxaline 4,9-dioxides (Xa-d) (Scheme 3). We note that the pyrrole ring under these conditions is formed rather quickly (the reaction is finished after 0.5-1.0 h) and is not accompanied by nucleophilic substitution of the fluorine atom. When the reaction of compound VII with an excess of ethylamine and methylamine is prolonged to 1.0-1.5 h (gas is passed through until the precipitate formation finishes), the formation of the pyrrole ring is accompanied by the replacement of the fluorine atom at $C_{(6)}$ to give the 6-aminosubstituted XIa, b. Convincing proof of the replacement of the fluorine atom on $C_{(6)}$ was obtained using two-dimensional ^1H-^{13}C NMR. The ^{13}C NMR spectrum of 2-ethyl-6-ethylamino-7-fluoro-1-oxo-1,3-dihydropyrrolo[3,4-*b*]quinoxaline 4,9-dioxide (XIb) with broad-band proton decoupling contains resonances of $C_{(4a)}$ and $C_{(9a)}$ that can be easily differentiated because $C_{(9a)}$ has a spin-spin

TABLE 1. Properties of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %	PMR spectrum, δ, ppm (SSCC, J, Hz)			
		C	H	N			5-H, 8-H	R	R^1	CH_3 (3H, s)
1	2	3	4	5	6	7	8	9	10	11
IIIa	$C_{11}H_8F_2N_2O_3$	52,04 / 51,97	3,39 / 3,17	11,17 / 11,02	184...185	72	8,44 (1H, dd, $^3J_{HF}$ = 10,5; $^4J_{HF}$ = 7,9) 8,53 (1H, dd, $^3J_{HF}$ = 10,1; $^4J_{HF}$ = 7,5)	2,65 (3H, s, CH_3)	—	2,50
IIIb	$C_{12}H_{10}F_2N_2O_4$	50,54 / 50,71	3,43 / 3,55	9,77 / 9,86	111...112	60	8,44 (1H, dd, $^3J_{HF}$ = 10,2; $^4J_{HF}$ = 7,6) 8,48 (1H, dd, $^3J_{HF}$ = 10,5; $^4J_{HF}$ = 7,6)	1,36 (3H, t, $C\underline{H}_3CH_2O$) 4,50 (2H, q, $CH_3C\underline{H}_2O$)	—	2,50
IIIc	$C_{16}H_{10}F_2N_2O_3$	60,95 / 60,76	3,34 / 3,19	9,03 / 8,86	191...192	64	8,41 (1H, dd, $^3J_{HF}$ = 10,1; $^4J_{HF}$ = 7,5) 8,54 (1H, dd, $^3J_{HF}$ = 10,5; $^4J_{HF}$ = 7,5)	7,67 (3H, m) 8,05 (2H, m) (C_6H_5)	—	2,31
IIId	$C_{16}H_{11}F_2N_3O_3$	58,21 / 58,01	3,56 / 3,35	12,76 / 12,69	220...221	60	8,50 (1H, dd, $^3J_{HF}$ = 8,8; $^4J_{HF}$ = 7,5) 8,60 (1H, dd, $^3J_{HF}$ = 9,2; $^4J_{HF}$ = 7,5)	7,38 (3H, m) 7,68 (2H, m) (C_6H_5) 10,94 (1H, s, NH)	—	2,51
IVa	$C_{15}H_{16}FN_3O_4$	56,24 / 56,07	5,05 / 5,02	12,86 / 13,08	212...213	60	7,80 (1H, d, 8-H, $^4J_{HF}$ = 8,4) 8,10 (1H, d, 5-H, $^3J_{HF}$ = 13,2)	2,64 (3H, s, CH_3)	3,32 [4H, m, $N(CH_2)_2$)]; 3,82 [4H, m, $O(CH_2)_2$)]	2,36
IVd	$C_{16}H_{18}FN_3O_5$	54,79 / 54,70	5,24 / 5,16	11,97 / 11,96	129...130	44	7,75 (1H, d, 8-H, $^4J_{HF}$ = 8,3) 8,07 (1H, d, 5-H, $^3J_{HF}$ = 13,0)	1,35 (3H, t, $C\underline{H}_3CH_2O$) 4,49 (2H, q, $CH_3C\underline{H}_2O$)	3,30 [4H, m, $N(CH_2)_2$)]; 3,81 [4H, m, $O(CH_2)_2$)]	2,42
IVg	$C_{20}H_{18}FN_3O_4$	62,51 / 62,66	4,77 / 4,73	10,80 / 10,96	255...256	58	7,84 (1H, d, 8-H, $^4J_{HF}$ = 8,2) 8,05 (1H, d, 5-H, $^3J_{HF}$ = 12,8)	7,57 (2H, m) 7,76 (1H, m) 8,01 (2H, m) (C_6H_5)	3,30 [4H, m, $N(CH_2)_2$)]; 3,83 [4H, m, $O(CH_2)_2$)]	2,31

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11
IVh	$C_{21}H_{21}FN_4O_3$	63,40 63,62	5,14 5,34	14,31 14,13	227...228	53	7,82 (1H, d, 8-H, $^4J_{HF}$ = 8,2) 8,03 (1H, d, 5-H, $^3J_{HF}$ = 13,1)	7,56 (2H, m) 7,75 (1H, m) 8,00 (2H, m) (C_6H_5)	2,51 (3H, s, NCH_3) 2,54 [4H, m, $N(CH_2)_2$)]; 3,30 [4H, m, $N(CH_2)_2$)]	2,29
IVi	$C_{20}H_{18}FN_3O_3$	65,20 65,39	4,65 4,94	11,46 11,44	232...233	54	7,33 (1H, d, 8-H, $^4J_{HF}$ = 8,2) 7,94 (1H, d, 5-H, $^3J_{HF}$ = 14,0)	7,56 (2H, m) 7,74 (1H, m) 7,95 (2H, m) (C_6H_5)	2,01 [4H, m, $N(CH_2)_2$)]; 3,60 [4H, m, $O(CH_2)_2$)]	2,28
IVj	$C_{20}H_{19}FN_4O_4$	60,08 60,29	4,83 4,81	14,07 14,06	246...247	44	7,83 (1H, d, 8-H, $^4J_{HF}$ = 8,3) 8,16 (1H, d, 5-H, $^3J_{HF}$ = 13,1)	7,18 (1H, m) 7,42 (2H, m) 7,67 (2H, m) (C_6H_5) 10,94 (1H, s, NH)	3,37 [4H, m, $N(CH_2)_2$)]; 3,82 [4H, m, $O(CH_2)_2$)]	2,49
Va	$C_{11}H_8F_2N_2O$	59,40 59,46	3,33 3,63	12,60 12,61	121	94	8,12 (1H, dd, $^3J_{HF}$ = 11,0; $^4J_{HF}$ = 8,6) 8,60 (1H, dd, $^3J_{HF}$ = 10,7; $^4J_{HF}$ = 8,2)	2,83 (3H, s, CH_3)	—	2,74
Vb	$C_{12}H_{10}F_2N_2O_2$	57,10 57,14	3,97 4,00	11,18 11,10	90...92	87	7,78 (1H, dd, $^3J_{HF}$ = 10,4; $^4J_{HF}$ = 7,9)*[2] 7,91 (1H, dd, $^3J_{HF}$ = 10,4; $^4J_{HF}$ = 8,2)	1,49 (3H, t, $C\underline{H}_3CH_2O$) 4,56 (2H, q, $CH_3C\underline{H}_2O$)	—	2,93
Vc	$C_{16}H_{10}F_2N_2O$	67,80 67,60	3,72 3,55	9,84 9,86	108...109	85	8,18 (1H, dd, $^3J_{HF}$ = 11,0; $^4J_{HF}$ = 8,6) 8,21 (1H, dd, $^3J_{HF}$ = 11,0; $^4J_{HF}$ = 8,5)	7,58 (2H, m) 7,74 (1H, m) 7,92 (2H, m) (C_6H_5)	—	2,70
Vd	$C_{16}H_{11}F_2N_3O$	64,27 64,21	3,94 3,71	13,82 14,04	170...171	81	8,18 (1H, dd, $^3J_{HF}$ = 11,3; $^4J_{HF}$ = 7,6) 8,25 (1H, dd, $^3J_{HF}$ = 11,0; $^4J_{HF}$ = 7,6)	7,17 (1H, m) 7,41 (2H, m) 7,81 (2H, m) (C_6H_5) 10,78 (1H, s, NH)	—	2,51

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11
VIa	$C_{15}H_{16}FN_3O_2$	62,13 62,27	5,55 5,58	14,34 14,52	164	86	7,36 (1H, d, 8-H, $^4J_{HF}$ = 8,9)*[2] 7,67 (1H, d, 5-H, $^3J_{HF}$ = 13,1)	2,93 (3H, s, CH_3)	3,32 [4H, m, $N(CH_2)_2$)]; 3,93 [4H, m, $O(CH_2)_2$)]	2,79
VIb	$C_{16}H_{19}FN_4O$	63,44 63,55	6,17 6,35	18,27 18,53	110...112	70	7,34 (1H, d, 8-H, $^4J_{HF}$ = 8,9)*[2] 7,63 (1H, d, 5-H, $^3J_{HF}$ = 13,3)	2,90 (3H, s, CH_3)	2,72 [4H, m, $N(CH_2)_2$)] 2,77 (3H, s, NCH_3) 3,37 [4H, m, $N(CH_2)_2$)]	2,40
VIc	$C_{15}H_{16}FN_3O$	65,70 65,91	5,67 5,91	15,06 15,38	125...126	80	6,96 (1H, d, 8-H, $^4J_{HF}$ = 9,3)*[2] 7,55 (1H, d, 5-H, $^3J_{HF}$ = 14,1)	2,91 (3H, s, CH_3)	2,05 [4H, m, $N(CH_2)_2$)]; 3,64 [4H, m, $N(CH_2)_2$)]	2,76
VId	$C_{16}H_{18}FN_3O_3$	60,25 60,18	5,94 5,68	13,25 13,16	134...135	78	7,35 (1H, d, 8-H, $^4J_{HF}$ = 8,9)*[2] 7,74 (1H, d, 5-H, $^3J_{HF}$ = 13,4)	1,48 (3H, t, $C\underline{H}_3CH_2O$) 4,53 (2H, q, $CH_3C\underline{H}_2O$)	3,31 [4H, m, $N(CH_2)_2$)]; 3,92 [4H, m, $O(CH_2)_2$)]	2,92
VIe	$C_{17}H_{21}FN_4O_2$	61,16 61,42	6,17 6,38	16,71 16,86	87...88	70	7,36 (1H, d, 8-H, $^4J_{HF}$ = 8,9)*[2] 7,72 (1H, d, 5-H, $^3J_{HF}$ = 13,4)	1,48 (3H, t, $C\underline{H}_3CH_2O$) 4,53 (2H, q, $CH_3C\underline{H}_2O$)	2,67 [4H, m, $N(CH_2)_2$)] 2,91 (3H, s, NCH_3) 3,37 [4H, m, $N(CH_2)_2$)]	2,40
VIf	$C_{16}H_{18}FN_3O_2$	63,07 63,35	5,86 6,00	13,64 13,86	121...122	64	6,92 (1H, d, 8-H, $^4J_{HF}$ = 9,2)*[2] 7,64 (1H, d, 5-H, $^3J_{HF}$ = 14,7)	1,47 (3H, t, $C\underline{H}_3CH_2O$) 4,51 (2H, q, $CH_3C\underline{H}_2O$)	2,45 [4H, m, $N(CH_2)_2$)]; 3,63 [4H, m, $N(CH_2)_2$)]	2,90
VIg	$C_{20}H_{18}FN_3O_2$	68,12 68,36	4,98 5,16	11,73 11,96	176...178	91	7,58 (1H, d, 8-H, $^4J_{HF}$ = 7,6) 7,82 (1H, d, 5-H, $^3J_{HF}$ = 13,7)	7,51 (2H, m) 7,73 (1H, m) 7,88 (2H, m) (C_6H_5)	3,27 [4H, m, $N(CH_2)_2$)]; 3,82 [4H, m, $O(CH_2)_2$)]	2,67

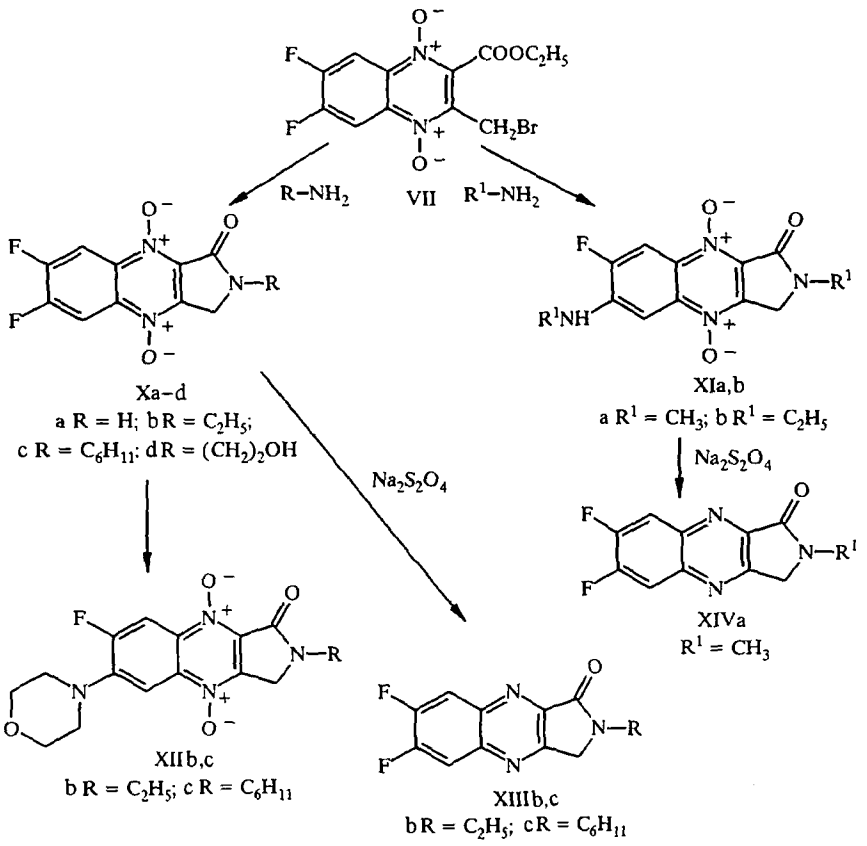
TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11
VIh	$C_{21}H_{21}FN_4O$	69,00 69,21	5,60 5,81	15,68 15,38	121...122	82	7,58 (1H, d, 8-H, $^4J_{HF}$ = 7,6) 7,80 (1H, d, 5-H, $^3J_{HF}$ = 13,7)	7,50 (2H, m) 7,72 (1H, m) 7,88 (2H, m) (C_6H_5)	2,55 [4H, m, $N(CH_2)_2$)] 2,67 (3H, s, NCH_3) 3,29 [4H, m, $N(CH_2)_2$)]	2,29
VIi	$C_{20}H_{18}FN_3O$	71,48 71,62	5,20 5,41	12,53 12,53	104...106	75	7,00 (1H, d, 8-H, $^4J_{HF}$ = 9,5) 7,67 (1H, d, 5-H, $^3J_{HF}$ = 14,7)	7,55 (2H, m) 7,70 (1H, m) 7,87 (2H, m) (C_6H_5)	1,99 [4H, m, $N(CH_2)_2$)]; 3,58 [4H, m, $N(CH_2)_2$)]	2,65
VIj	$C_{20}H_{19}FN_4O_2$	65,41 65,57	5,08 5,19	15,39 15,30	197...198	61	7,50 (1H, d, 8-H, $^4J_{HF}$ = 9,2) 7,88 (1H, d, 5-H, $^3J_{HF}$ = 13,7)	7,15 (1H, m) 7,39 (2H, m) 7,82 (2H, m) (C_6H_5) 10,67 (1H, s, NH)	3,35 [4H, m, $N(CH_2)_2$)]; 3,83 [4H, m, $O(CH_2)_2$)]	2,84
VIk	$C_{21}H_{22}FN_5O$	66,46 66,47	6,00 5,85	18,31 18,46	140...141	60	7,41 (1H, d, 8-H, $^4J_{HF}$ = 7,7)*[2] 7,64 (1H, d, 5-H, $^3J_{HF}$ = 13,4)	7,16 (1H, m) 7,39 (2H, m) 7,77 (2H, m) (C_6H_5) 9,92 (1H, s, NH)	2,65 [4H, m, $N(CH_2)_2$)] 3,11 (3H, s, NCH_3) 3,37 [4H, m, $N(CH_2)_2$)]	2,39
VIl	$C_{20}H_{19}FN_4O$	68,40 68,50	5,50 5,47	15,73 15,99	160...162	64	6,98 (1H, d, 8-H, $^4J_{HF}$ = 9,2) 7,75 (1H, d, 5-H, $^3J_{HF}$ = 14,7)	7,13 (1H, m) 7,38 (2H, m) 7,82 (2H, m) (C_6H_5) 10,56 (1H, s, NH)	1,99 [4H, m, $N(CH_2)_2$)]; 3,58 [4H, m, $N(CH_2)_2$)]	2,81

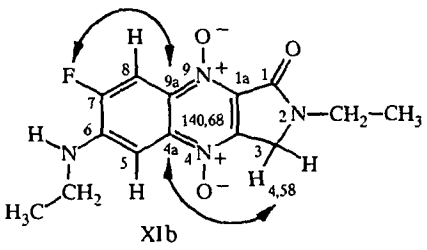
* Compounds IIIa; IVd, i; Va, b, d; and VIa, g - l were recrystallized from ethanol; IIIb, from water; VIb, e, from hexane; IIIc, d, IVg, h, and VIc, f, from a DMF–ethanol mixture; IVa, j, from DMF.

*[2] Spectra are recorded in $CDCl_3$; all others, in DMSO-d_6.

Scheme 3



coupling constant (SSCC) with 7-F ($^3J_{CF}$ = 14.4 Hz) whereas $C_{(4a)}$ exhibits no coupling with 7-F. By using the COLOC pulse sequence for two-dimensional ^1H-^{13}C NMR, which enables long range SSCC to be observed, we established the link between $C_{(3)}$ protons with δ = 4.58 ppm and $C_{(4a)}$ protons with δ = 140.68 ppm. This completely agrees with the structure of XIb.



The susceptibility of the fluorine atom at $C_{(6)}$ in fluorinated pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides to nucleophilic substitution is illustrated by the reaction of compounds Xb and c with morpholine, which forms at room temperature the 2-substituted 7-fluoro-6-morpholino-1-oxo-1,3-dihydro-2H-pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides (XIIb, c) in 65-75% yields.

The N-oxides in the fluorinated pyrroloquinoxaline 4,9-dioxides Xb, c and XIa can be easily reduced by sodium dithionite to give the corresponding pyrroloquinoxalines XIIIb, c and XIVa.

Thus, the reaction of 5,6-difluorobenzofuroxan with enolates is a convenient method for synthesis of fluorine-substituted quinoxaline 1,4-dioxides and the furo[3,4-*b*]- and pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides derived from them. The facile nucleophilic substitution of the fluorine atom in these compounds and the ability of the N-oxides to be reduced can be used for further structural modification of the condensed quinoxalines.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on Bruker WH-250 and LRX-500 spectrometers in DMSO-d_6, $CDCl_3$, and CD_3CN with TMS as internal standard. Chemical shifts are given as δ in ppm. The characteristics of the synthesized compounds and the ^1H NMR data are listed in Table 1.

2-RCO-6,7-Difluoro-3-methylquinoxaline 1,4-Dioxides (IIIa-d). Suspension of 5,6-difluorobenzofuroxan I (10 mmol) in triethylamine (10 ml) is treated with a 1,3-dicarbonyl compound IIa-d (10-12 mmol) at 0-5°C. The reaction mixture is stirred for 1 h at 0-10°C, 1 h at room temperature, and then cooled to 0°C. An oily precipitate begins to form. After adding water (20 ml) and stirring the reaction mixture for 1 h at 5-10°C, the crystalline precipitate is filtered off, washed on the filter with water, dried and recrystallized from the appropriate solvent.

2-RCO-6-R^1-7-Fluoro-3-methylquinoxaline 1,4-Dioxides (IVa, d, g - j). Compound IIa-d (10-12 mmol) was added to suspension of 5,6-difluorobenzofuroxan I (10 mmol) in abs. ethanol or dioxane (30 ml). Then a cyclic imine (20 mmol) was added dropwise. The yellow-brown solution is stirred at room temperature for 2-10 h. The yellow precipitate is filtered off, washed on the filter with cold ethanol, dried, and recrystallized.

2-RCO-6,7-Difluoro-3-methylquinoxalines (Va-d). Solution of compound IIIa or IIIb (2 mmol) in ethanol (60%, 20 ml) [IIIc, d in an ethanol–DMF mixture (20 ml, 2:1)] is treated portionwise with $Na_2S_2O_4$ (1.4 g, 8 mmol) in water (5 ml). The reaction mixture is heated on a water bath for 2-3 h at 75-80°C (overheating is unallowable!) and cooled. Water (50 ml) is added. The colorless precipitate is filtered off, washed with water, dried, and recrystallized.

2-RCO-6-R^1-7-Fluoro-3-methylquinoxalines (VIa, d, g - j). $Na_2S_2O_4$ (1.4 g, 8 mmol) in water (5 ml) was added portionwise to boiling solution of compound IVa, d, g - j (2 mmol) in ethanol–DMF mixture (20 ml, 2:1). The reaction mixture is boiled for 3 h, cooled, and poured into water (50 ml). The crystalline precipitate is filtered off, washed with water, dried, and recrystallized.

2-RCO-6-R^1-Fluoro-3-methylquinoxaline (VIb, c, e, f, k, l). Solution of compound IVb, c, e, f, k, l (2 mmol) in DMF (10 ml) is treated with a cyclic imine (6 mmol) and heated at 110-115°C for 1 h. The reaction mixture is cooled and poured into water (50 ml). The crystalline precipitate is filtered off, washed with water, dried, and recrystallized.

3-Bromomethyl-2-ethoxycarbonyl-6,7-difluoroquinoxaline 1,4-Dioxide (VII). Solution of bromine (0.6 ml, 11.2 mmol) in $CHCl_3$ (2 ml) is added dropwise to solution of 2-ethoxycarbonyl-6,7-difluoro3-methylquinoxaline 1,4-dioxide IIIb (2.8 g, 10 mmol) in DMF (18 ml) previously heated to 80°C. The reaction mixture is stirred at 80-90°C for 0.5 h, cooled to room temperature, and poured onto ice. The yellow oil obtained is recrystallized from propan-2-ol. Yield 3.3 g (92%); mp 136-137°C. ^1H NMR (DMSO-d_6): 1.38 (3H, t, $\underline{CH_3}CH_2O$), 4.54 (2H, q, $CH_3\underline{CH_2}O$), 4.69 (2H, s, CH_2Br), 8.45 (1H, dd, $^3J_{HF}$ = 9.9, $^4J_{HF}$ = 7.6 Hz), and 8.60 (1H, dd, $^3J_{HF}$ = 9.9, $^4J_{HF}$ = 7.3 Hz) (5-H and 8-H). Found, %: C 40.01; H 2.69; N 7.89. $C_{12}H_9BrF_2N_2O_4$. Calculated, %: C 39.65; H 2.48; N 7.71.

3-Acetoxymethyl-2-ethoxycarbonyl-6,7-difluoroquinoxaline 1,4-Dioxide (VIII). Solution of acetic acid (1.3 ml, 21.6 mmol) is treated dropwise with triethylamine (2.9 ml, 21 mmol) in acetone (37 ml) at 20-25°C. After 15 min the resulting solution is treated portionwise over 10-15 min with bromomethyl compound VII (2.0 g, 5.5 mmol). The reaction mixture is stirred at room temperature for 1.5-2.0 h. The precipitate of triethylamine hydrobromide is filtered off. The filtrate is diluted with water (40 ml) and neutralized with aqueous $NaHCO_3$ until the pH 7. The yellow precipitate of VIII is filtered off, washed with water, and recrystallized from ethanol (60%). Yield 1.5 g (80%); mp 119-120°C. ^1H NMR (DMSO-d_6): 1.35 (3H, t, $\underline{CH_3}CH_2O$), 2.07 (3H, s, $CH_2OCO\underline{CH_3}$), 4.48 (2H, q, $CH_3\underline{CH_2}O$), 5.37 (2H, s, $\underline{CH_2}OCOCH_3$), 8.48 (1H, dd, $^3J_{HF}$ = 10.5, $^4J_{HF}$ = 7.7 Hz), and 8.52 (1H, dd, $^3J_{HF}$ = 10.1, $^4J_{HF}$ = 7.7 Hz) (5-H and 8-H). Found, %: C 49.30; H 3.53; N 8.43. $C_{14}H_{12}F_2N_2O_6$. Calculated, %: C 49.12; H 3.51; N 8.19.

6,7-Difluoro-1-oxo-1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-Dioxide (IX). Suspension of compound VIII (3.0 g, 9 mmol) in conc. HCl (14 ml) is held at room temperature for 18 h and cooled in an ice bath. The bright yellow precipitate of the lactone IX is filtered off. The filtrate is diluted with absolute ethanol (25-30 ml) in order to isolate an additional amount of IX. The isolated precipitates are combined and recrystallized from acetic acid.

Yield 2.1 g (92%); mp 234-235°C. ^{1}H NMR (DMSO-d_6): 5.50 (2H, s, $\underline{CH_2}$), 8.59 (1H, dd, $^3J_{HF}$ = 10.2, $^4J_{HF}$ = 7.5 Hz), and 8.65 (1H, dd, $^3J_{HF}$ = 10.4, $^4J_{HF}$ = 7.3 Hz) (5-H and 8-H). Found, %: C 47.44; H 1.43; N 11.10. $C_{10}H_4F_2N_2O_4$. Calculated, %: C 47.24; H 1.57; N 11.02.

2-R-6,7-Difluoro-1-oxo-1,3-dihydropyrrolo[3,4-*b*]quinoxaline 4,9-Dioxides (Xa, b). An excess of dry amine is passed through solution of the compound VII (2 mmol) in dry acetonitrile for 25-30 min at 10-15°C. The yellow precipitate is filtered off, dried, and recrystallized. Characteristics for compound Xa: yield 96%; mp 234-235°C (acetonitrile–ethanol, 1:3). ^{1}H NMR (DMSO-d_6): 4.49 (2H, s, $\underline{CH_2}$), 8.54 (1H, dd, $^3J_{HF}$ = 9.2, $^4J_{HF}$ = 7.66 Hz) and 8.59 (1H, dd, $^3J_{HF}$ = 9.5, $^4J_{HF}$ = 7.6 Hz) (5-H and 8-H), 9.20 ppm (1H, br. s, NH). Found, %: C 47.03; H 2.08; N 16.37. $C_{10}H_5F_2N_3O_3$. Calculated, %: C 47.43; H 1.98; N 16.60. Compound Xb: yield 76%; mp 217-218°C (ethanol). ^{1}H NMR (CD_3CN): 1.25 (3H, t, $CH_2\underline{CH_3}$), 3.32 (2H, q, $\underline{CH_2}CH_3$), 4.54 (2H, s, CH_2), 8.43 (1H, dd, $^3J_{HF}$ = 10.2, $^4J_{HF}$ = 7.5 Hz) and 8.47 ppm (1H, dd, $^3J_{HF}$ = 10.4, $^4J_{HF}$ = 7.5 Hz) (5-H and 8-H). Found, %: C 51.04; H 3.36; N 15.08. $C_{12}H_9F_2N_3O_3$. Calculated, %: C 51.24; H 3.20; N 14.95.

2-R-6,7-Difluoro-1-oxo-1,3-dihydropyrrolo[3,4-b]quinoxaline 4,9-Dioxides (Xc, d). An amine (2.8 mmol) is slowly added to solution of the bromoderivative VII (1.4 mmol) in dry acetonitrile (15 ml). The reaction mixture is stirred at room temperature for 0.5-1.0 h. The yellow precipitate is filtered off, dried, and recrystallized. Compound Xc: yield 87%; mp 220-221°C (ethanol–DMF, 1:3). ^{1}H NMR (DMSO-d_6): 1.49 [10H, m, $(CH_2)_5$], 4.00 (1H, m, CH), 4.59 (2H, s, CH_2), 8.55 (1H, dd, $^3J_{HF}$ = 10.2, $^4J_{HF}$ = 7.4 Hz) and 8.57 ppm (1H, dd, $^3J_{HF}$ = 10.5, $^4J_{HF}$ = 7.4 Hz) (5-H and 8-H). Found, %: C 56.95; H 4.50; N 12.31. $C_{16}H_{15}F_2N_3O_3$. Calculated, %: C 57.31; H 4.48; N 12.54. Compound Xd: yield 94%; mp 192-193°C (ethanol). ^{1}H NMR (DMSO-d_6): 3.62 [4H, m, $(\underline{CH_2})_2OH$], 4.68 (2H, s, CH_2), 4.85 [1H, t, $(CH_2)_2\underline{OH}$], 8.54 (1H, dd, $^3J_{HF}$ = 10.4, $^4J_{HF}$ = 7.6 Hz) and 8.60 ppm (1H, dd, $^3J_{HF}$ = 10.4, ^4J = 7.6 Hz) (5-H and 8-H). Found, %: C 48.60; H 3.12; N 13.95. $C_{12}H_9F_2N_3O_4$. Calculated, %: C 48.48; H 3.03; N 14.14.

2-R^1-6-R^1-Amino-7-fluoro-1-oxo-1,3-dihydropyrrolo[3,4-*b*]quinoxaline 4,9-Dioxides (XIa, b). An excess of dried amine is passed through solution of the compound VII (2 mmol) in dry acetonitrile (50 ml) for 1.0-1.5 h at 10-15°C. The yellow precipitate is filtered off, dried, and recrystallized. Compound XIa: yield 87%; mp 221-222°C (acetonitrile). ^{1}H NMR (DMSO-d_6): 2.92 (3H, d, $NH\underline{CH_3}$, ^3J = 4.9), 3.05 (3H, s, $N\underline{CH_3}$), 4.54 (2H, s, CH2), 7.23 (1H, d, 4JHF = 7.9 Hz, 5-H), 7.39 (1H, br. s, NH), 8.06 ppm (1H, d, 3JHF = 11.9 Hz). Found, %: C 52.16; H 4.25; N 20.20. C12H11FN4O3. Calculated, %: C 51.80; H 3.96; N 20.14. Compound XIb: yield 67%; mp 223-225°C (acetonitrile). ^{1}H NMR (DMSO-d_6): 1.20 (6H, m, two $NHCH_2\underline{CH_3}$), 3.32 (2H, m, $NH\underline{CH_2}CH_3$), 3.53 (2H, q, $N\underline{CH_2}CH_3$), 4.55 (2H, s, CH_2), 7.27 (1H, d, $^4J_{HF}$ = 7.9 Hz, 5-H), 7.30 (1H, br. s, NH), 8.04 ppm (1H, d, $^3J_{HF}$ = 11.9 Hz, 8-H). ^{13}C NMR ($CDCl_3$): 12.98 (s) and 13.83 (s) two $NCH_2\underline{CH_3}$), 37.52 (s) and 38.13 (s) (two $N\underline{CH_2}CH_3$), 44.10 (s, CH_2), 95.55 (d, C-5, $^3J_{CF}$ = 4.5 Hz), 105.22 (d, C-8, $^2J_{CF}$ = 26.7 Hz), 127.95 (s, C-3a), 132.43 (d, C-6, $^2J_{CF}$ = 11.0 Hz), 137.87 (s, C-1a), 140.68 (s, C-4a), 142.24 (d, C-9a, $^3J_{CF}$ = 14.4 Hz), 154.12 (d, C-7, $^1J_{CF}$ = 254.7 Hz), 158.68 ppm (s, C-1). Found, %: C 54.81; H 4.95; N 18.50. $C_{14}H_{15}FN_4O_3$. Calculated, %: C 54.90; H 4.90; N 18.30.

2-R^1-7-Fluoro-6-morpholino-1-oxo-1,3-dihydropyrrolo[3,4-*b*]quinoxaline 4,9-Dioxides (XIIb, c). Morpholine (2 mmol) is added to a suspension of compound Xb or Xc (3 mmol) in abs. ethanol or DMF (20-25 ml). The reaction mixture is stirred at room temperature for 3-4 h. The bright yellow precipitate is filtered off and recrystallized from ethanol. Compound XIIb: yield 65%; mp 222-223°C. ^{1}H NMR (DMSO-d_6): 1.20 (3H, t, $CH_2\underline{CH_3}$), 3.32 [4H, m, $N(CH_2)_3$], 3.54 (2H, q, $\underline{CH_2}CH_3$), 3.81 [4H, m, $O(CH_2)_2$], 7.75 (1H, d, $^4J_{HF}$ = 8.2 Hz), 8.17 ppm (1H, d, $^3J_{HF}$ = 13.4 Hz, 8-H). Found, %: C 54.94; H 4.61; N 15.83. $C_{16}H_{17}FN_4O_4$. Calculated, %: C 55.17; H 4.89; N 16.09. Compound XIIc: yield 75%; mp 205-206°C. ^{1}H NMR (DMSO-d_6): 1.49 [10H, m, $(CH_2)_5$], 3.38 [4H, m, $N(CH_2)_2$], 3.80 [4H, m, $O(CH_2)_2$], 4.00 (1H, m, CH), 4.55 (2H, s, CH_2), 7.76 (1H, d, $^4J_{HF}$ = 8.2 Hz, 5-H), 8.18 ppm (1H, d, $^3J_{HF}$ = 13.4 Hz, 8-H). Found, %: C 59.64; H 5.80; N 13.83. $C_{20}H_{23}FN_4O_4$. Calculated, %: C 59.70; H 5.72; N 13.93.

Method for Reduction of Compounds Xb,c, and XIa. $Na_2S_2O_4$ (4 mmol) in water (10 ml) is added portionwise to a suspension of the dioxide Xb, c, or XIa (1 mmol) in ethanol (50%, 10-15 ml). The reaction mixture is heated on a water bath for 0.5-1.5 h and cooled. The product is filtered off or precipitated by addition of water (50-60 ml), dried, and recrystallized from ethanol. Compound XIIIb: yield 54%; mp 246-247°C. ^{1}H NMR (DMSO-d_6): 1.27 (3H, t, $CH_2\underline{CH_3}$), 3.70 (2H, q, $\underline{CH_2}CH_3$), 4.72 (2H, s, CH_2), 8.29 (1H, dd, $^3J_{HF}$ = 11.4, $^4J_{HF}$ = 8.6 Hz)

and 8.38 ppm (1H, dd, $^3J_{HF}$ = 11.0, $^4J_{HF}$ = 8.3 Hz) (5-H and 8-H). Found, %: C 57.61; H 3.53; N 16.57. $C_{12}H_9F_2N_3O$. Calculated, %: C 57.83; H 3.61; N 16.87. Compound XIIIc: yield 46%; mp 220-221°C. ^{1}H NMR (DMSO-d_6): 1.51 [10H, m, $(CH_2)_5$], 4.20 (1H, m, CH), 4.68 (2H, s, CH_2), 8.31 (1H, dd, $^3J_{HF}$ = 11.3, $^4J_{HF}$ = 11.3, $^4J_{HF}$ = 8.2 Hz) and 8.40 ppm (1H, dd, $^3J_{HF}$ = 11.0, $^4J_{HF}$ = 8.2 Hz) (5-H and 8-H). Found, %: C 63.10; H 4.90; N 13.86. $C_{16}H_{15}F_2N_3O$. Calculated, %: C 63.37; H 4.95; N 13.86. Compound XIVa: yield 48%; mp 221-222°C. ^{1}H NMR (DMSO-d_6): 2.91 (3H, d, $NHCH_3$, ^{3}J = 4.9 Hz), 3.18 (3H, s, NCH_3), 4.56 (2H, s, CH_2), 6.95 (1H, d, $^4J_{HF}$ = 9.2 Hz, 5-H), 7.00 (1H, br. s, NH), 7.78 ppm (1H, d, $^3J_{HF}$ = 12.5 Hz, 8-H). Found, %: C 58.70; H 4.63; N 22.54. $C_{12}H_{11}FN_4O$. Calculated, %: C 58.54; H 4.47; N 22.76.

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