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5(6)-Fluoro-6(5)-*R*-benzofuroxans: synthesis and NMR ^{1}H, ^{13}C and ^{19}F studies

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Abstract

5(6)-Fluoro-6(5)-substituted benzofuroxans were obtained by the reactions of 5,6-difluorobenzofuroxan with a number of nucleophiles, such as alkylamines, cycloalkylimines, sodium azide and sodium alkoxides. The features of tautomerism in the series of asymmetrical 5(6)-fluorobenzofuroxans in acetone solutions have been studied by ^{1}H, ^{13}C and ^{19}F NMR.

Keywords: 5,6-Difluorobenzofuroxan; Nucleophilic substitution; ^{1}H, ^{13}C and ^{19}F NMR; X-ray crystallography

1. Introduction

Furoxans comprise a well-known class of heterocyclic compounds which proved to exhibit a variety of biological activities [1]. The ability of benzofuroxans to be involved in the synthesis of DNA and peptides has stimulated a search aimed at the development of anticancer compounds [2]. Furoxans are also of interest as cardiovascular agents (like nitroglicerol) due to their ability to generate nitrous oxide and to effect the level of guanilate-cyclase [3].

Fluorinated benzofuroxans are of special interest, since fluorine atoms are known to increase the ability of organic compounds to penetrate thorough lipid membranes, thus making these molecules more potent as biologically active compounds [4,5]. The ability of fluorine atoms in aromatics to be displaced by nucleophiles has been well documented in the literature [4–6]. We have recently described the features of nucleophilic displacement reactions in 6,7-difluoroquinoxalines [7,8]. In this paper we wish to present the data of our studies on the synthesis and tautomerism of asymmetrical 5(6)-fluoro-6(5)-substituted benzofuroxans derived from the reaction of 5,6-difluorobenzofuroxan with nucleophiles, such as cycloalkylimines, alkylamines, sodium azide and sodium alkoxides. Also the synthesis and ^{1}H, ^{13}C and ^{19}F NMR spectral parameters of 5-fluoro-6-substituted benzofurazans regarded as the model compounds for studying tautomerism will be discussed.

2. Results and discussion

The main synthetic routes to benzofuroxans are known to be oxidation of *ortho*-nitroanilines, oxidation of *ortho*-quinone dioximes or decomposition of *ortho*-nitroaryl-azides [9a–c]. It has been established that benzofuroxans rearrange rapidly in solutions between two asymmetrical structures through opening of the oxadiazole ring and intermediacy of the dinitroso compound [9a–f].

5,6-Difluorobenzofuroxan (**1**) was obtained in good yield by decomposition of 4,5-difluoro-2-nitrophenylazide [10]. Compound **1** was shown to exist in acetone solutions as a mixture of two degenerated forms **1a** and **1b**, inter-converting to each other rapidly through intermediacy of the dinitroso compound (Scheme 1).

The reaction of 5,6-difluorobenzofuroxan (**1**) with morpholine in ethanol was found to proceed smoothly at room temperature (20–25 °C) for 2–3 h to give the nucleophilic substitution product **2** in 75–80% yield. The intensive peak of the molecular ion $(M)^{+}$, *m*/*z* (related intensity): 239 (1 0 0) in the mass-spectra of **2a** corresponds to the structure of the mono-substitution product. In the crystalline state compound **2a** was found to exist as 5-fluoro-6-morpholino-benzofuroxan (**2A**) (Fig. 1). The X-ray crystallography analysis of compound **2a** has revealed that the benzofuroxan

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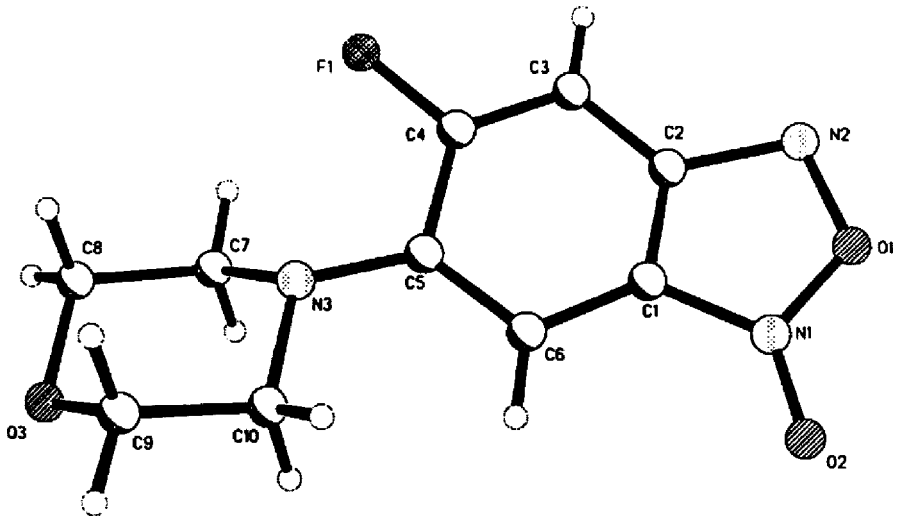
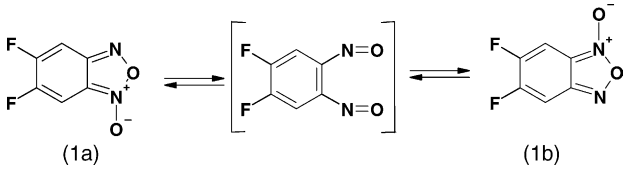


Fig. 1. A view of 5-fluoro-6-morpholinobenzofuroxan **2** (X-ray analysis data).



Scheme 1.

skeleton is planar, while the morpholine fragment is in a chair conformation with N-3 and O-3 atoms deviating from an average plane of the morpholine ring. The N-3–C-3 bond has a pseudo-equatorial orientation relative to the morpholine ring. The main geometrical parameters of **2A** are very close to those found for unsubstituted benzofuroxans [11] and appear to be common for nitrogen-containing heterocyclic systems [12].[1]

In the ^{1}H NMR spectrum of **2a** in $(CD_3)_2CO$ recorded at 20 °C the signals of H-4 and H-7 proved to be rather broadened (Fig. 2). We suggest that the compound **2a** exists as a mixture of two inter-converting forms **2A** and **2B**. In order to obtain the isomeric form **2B** we have performed the synthesis of 6-fluoro-5-morpholinobenzofuroxan (**2B**) by oxidation of the corresponding *ortho*-nitroaniline (Scheme 2).

The TLC data and ^{1}H and ^{19}F NMR spectra of compound **2B** were identical to those for sample **2a** obtained from 5,6-difluorobenzofuroxan (**1**), thus showing that compound **2B**, in solution, undergoes the molecular rearrangement into **2A**.

The ^{1}H, ^{13}C, and ^{19}F NMR spectra, recorded in $(CD_3)_2CO$ at the range of temperatures from −40 to +30 °C have shown that two isomeric compounds, 5-fluoro-6-morpholinobenzofuroxan (**2A**) and 6-fluoro-5-morpholinobenzofuroxan (**2B**), inter-converting to each other are present in the mixture (Scheme 2).

In the ^{1}H NMR spectra of **2a** recorded at −20 °C two doublet of doublets corresponding to H-4 and H-7 protons of isomers **2A** and **2B** with characteristic values of coupling constants $^3J_{H,F}$ and $^4J_{H,F}$ were observed.

The following coupling constants were measured for **2A**: ^3J(H4-F5) = 12.2 Hz, and ^4J(H7-F5) = 7.7 Hz, while **2B** exhibited ^3J(H7-F6) = 11.0 Hz, and ^4J(H4-F6) = 7.6 Hz (Table 1). The ratio of isomers **2A**:**2B** was (70:30). Increasing temperature up to 0 °C resulted in broadening of H-4 and H-7 signals; coalescence of these signals was observed at 20–25 °C (Fig. 2).

The ^{19}F NMR spectra of **2a**, recorded at the temperature range −20 to +20 °C gave a similar picture (Fig. 3). The coupling constants ^3J(F5-H4) = 12.2 Hz and ^4J(F5-H7) = 7.7 Hz were measured for the isomer **2A**, while **2B** gave ^3J(F6-H7) = 11.0 Hz and ^4J(F6-H4) = 7.6 Hz. The same ratio of isomers **2A**:**2B** (70: 30) was found.

The ^{1}H and ^{19}F NMR data, however, are not sufficient to conclude which isomer, **2A** or **2B** is dominant. Evidence in favor of the major isomer **2A** and unequivocal assignments of signals for isomers **2A** and **2B** were made on the basis of ^{13}C NMR spectra recorded at low temperatures.

Due to a slow exchange process at −20 °C two sets of characteristic signals corresponding to the ring junction carbons C-3a and C-7a of isomers **2A** and **2B** were observed in the ^{13}C NMR spectra of **2a**. The doublet at δ = 151.0 ppm was assigned to the quaternary carbon C-3a of **2A** due to the coupling constant ^3J(C3a-F5) = 14.1 Hz, while the resonance signal of C-7a was observed as a singlet at δ = 113.3 ppm. In the case of isomer **2B** the doublet of C-7a at δ = 111.6 ppm (^3J(C7*a*-F6) = 13.5 Hz) and the singlet of C-3a at δ = 152.1 ppm were observed in the spectra (Table 1).

According to all NMR measurements (^{1}H, ^{13}C and ^{19}F spectra) it is clear that an exchanging system of two isomeric

[1] Crystallographic data (excluding structure factors) for structure **2** in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

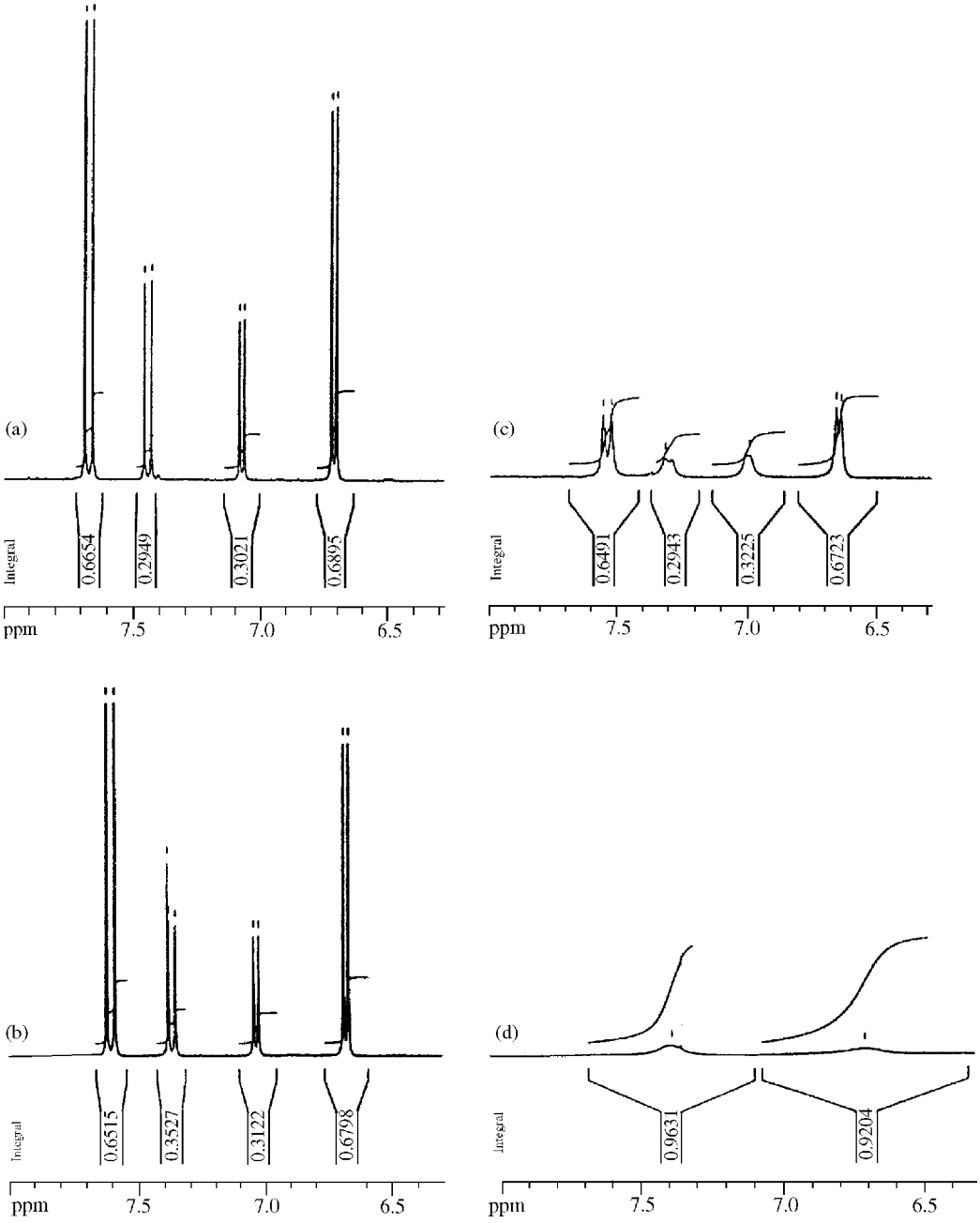
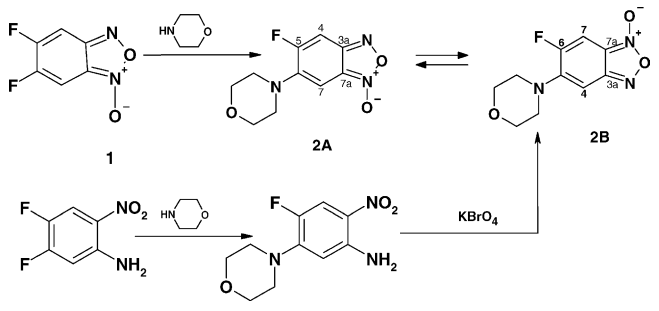


Fig. 2. ^{1}H NMR spectra of **2** in $(CD_3)_2CO$ recorded at −4 °C (a); −20 °C (b); 0 °C (c) and 20 °C (d).



Scheme 2.

compounds with unequal populations is present. From chemical shifts differences for H-4 and H-7 protons and population difference of **2A** and **2B** we have obtained free activation energies using the approximation method suggested by M. Õki [13] and Shanan-Atidi and Bar-Eli [14]. ΔG^* was estimated as 62.2 kJ mol^{-1} for transfer from **2A** to **2B**, and 59.1 kJ mol^{-1} for the reverse process.

Pyrrolidine, methylpiperazine and thiomorpholine were found to react with **1** in ethanol at 20 °C in a similar manner, affording amino compounds **2a–d** (Scheme 3). Also the reaction of **1** with methylamine or ethylamine in ethanol at room temperature resulted in the formation of the

Table 1
^{13}C, ^{19}F and ^{1}H NMR spectral data for compound **2a** (CD_3COCD_3, $T = -20$ °C)

2A				**2B**			
Carbon	$\delta(^{13}C)$ (ppm)	$^{n}J_{C\text{-}F}$ (Hz)	$\delta(^{1}H$ or $^{19}F)$ (ppm)	Carbon	$\delta(^{13}C)$ (ppm)	$^{n}J_{C\text{-}F}$ (Hz)	$\delta(^{1}H$ or $^{19}F)$ (ppm)
C5	161.43	262.7	107.42 m (12.2, 7.7)	C6	158.78	262.7	110.65 m (11.0, 7.6)
C3a	151.01	14.1	–	C7a	111.60	13.5	–
C6	145.47	16.2	–	C5	148.23	15.5	–
C7a	113.27	–	–	C3a	152.12	–	–
C4	102.29	28.3	7.60 d (12.2)	C7	97.77	31.0	7.37 d (11.0)
C7	96.55	4.0	6.68 d (7.7)	C4	101.48	3.4	7.03 d (7.6)
OCH_2	66.80	–	3.83 m	OCH_2	66.383	–	3.83 m
NCH_2	51.54	4.7	3.22 m	NCH_2	51.47	4.7	3.22 m

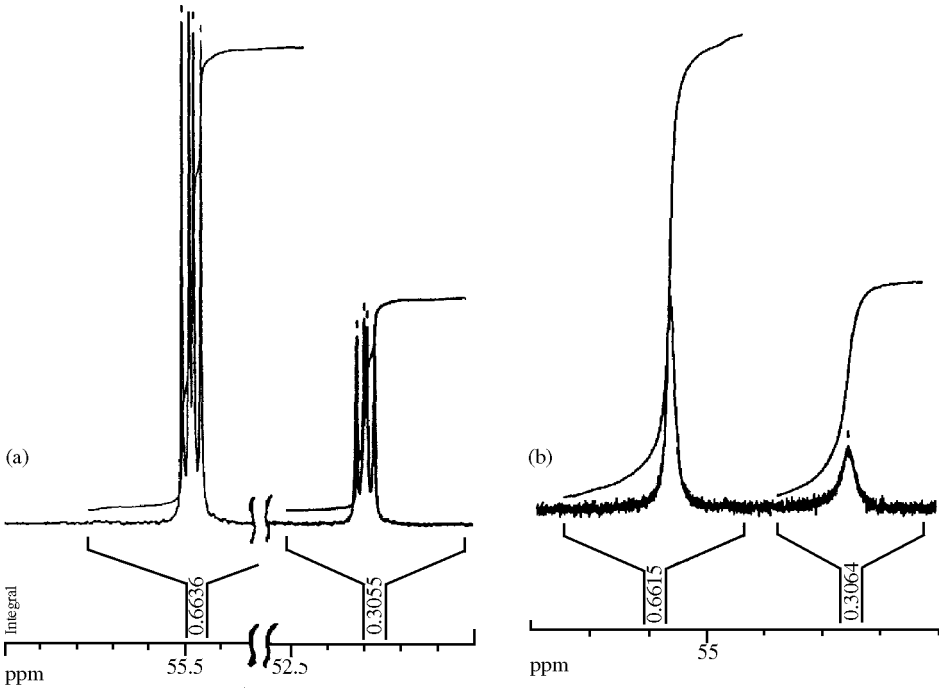


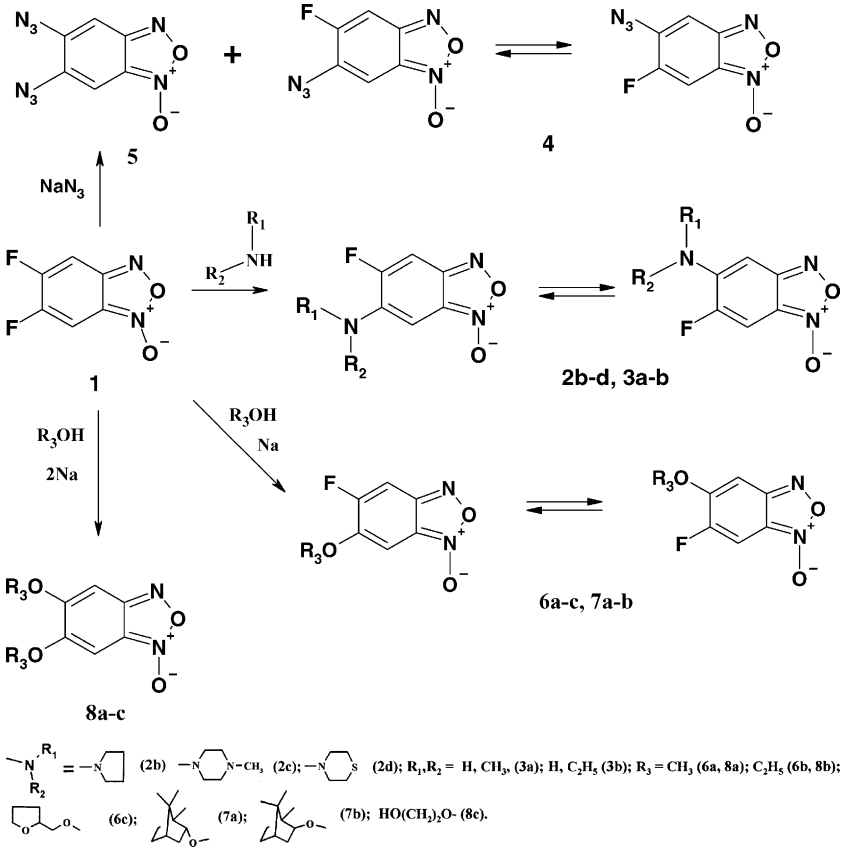
Fig. 3. ^{19}F NMR spectra of **2** in $(CD_3)_2CO$ recorded at −20 °C (a) and 0 °C (b).

corresponding amino compounds **3a–b** in good yields. Evidence for substitution of one of two fluorine atoms in **1** by action of amines is provided by elemental analyses and mass-spectrometry data for compounds **2b–d**, **3a–b** (see Section 3). In the ^{1}H NMR spectra of **2b–d**, **3a–b** ($(CD_3)_2SO$) recorded at room temperature, the signals of H-4 and H-7 protons are broadened due to the equilibrium.

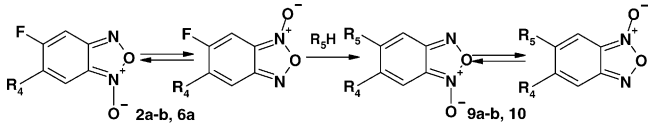
The reaction of 5,6-difluorobenzofuroxan (**1**) with sodium azide in ethanol affords mono-azido derivative **4** as minor product (yields 20–25%), while the major product is 5,6-diazidobenzofuroxan (**5**) which is formed even at the ratio of reagents 1:1. The composition of mono- and diazido substituted benzofuroxanes **4**, **5** is in agreement with their mass-spectra which have intensive molecular ions peaks $[M]^+$, *m/z* (relative intensity): 218 (92) and 195 (43), respectively. In the ^{1}H NMR spectrum of **5** in $(CD_3)_2SO$ recorded at room temperature H-4 and H-7 protons give rise to a singlet at 7.50 ppm, and in case of **4** two broadened singlets centered at 7.57 and 7.64 ppm are observed due to the established inter-conversions of the oxadiazole ring.

The reaction of 5,6-difluorobenzofuroxan (**1**) with alkoxides results in mono- or dialkoxy derivatives with the ratio being dependent on quantity of sodium taken for preparing alkoxides (Scheme 5, see Section 3). The reactions of **1** with sodium azide and sodium alkoxides indicate that the ability of both fluorine atoms at C-6 and C-5 positions to be displaced with nucleophiles is quite good.

In order to estimate relative reactivity of fluorine atoms to undergo nucleophilic substitution reactions we have studied the behavior of 5(6)-fluoro-6(5)-methoxybenzofuroxan (**6a**) under the action of morpholine and behavior of 5(6)-fluoro-6(5)-cycloalkyliminobenzofuroxans (**2a–b**) under the action of methanol (Scheme 4). Compound **6a** was found to react with morpholine only at an elevated temperature to give



Scheme 3.

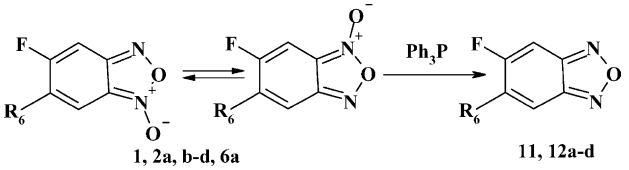


R_4=morpholinyl (**2a**); pyrrolidinyl (**2a**); methoxy (**6a**); R_4=methoxy, R_5=morpholinyl (**9a**); R_4=methoxy, R_5=pyrrolidinyl (**9b**); R_4=morpholinyl, R_5=methoxy (**10**)

Scheme 4.

5(6)-morpholino-6(5)-methoxybenzofuroxan (**9a**) in 80% yield after 2 h of reflux in ethanol. The same product **9a** was obtained by reaction of compound **2a** with methanol for 1.5 h (Scheme 5).

The data obtained show that fluorinated benzofuroxans are easily rearranged between two asymmetrical N-oxide structures through ring opening and closure of the oxadiazole ring in solutions. In order to confirm that N-deoxygenation of furoxans will destroy these inter-conversions, 5,6-difluorobenzofurazan (**11**) and 5-fluoro-6-substituted benzofurazans (**12a–d**) have been obtained from the corresponding furoxans **1, 2a**, **2c–d**, **6a** on treatment with triphenylphospine, as evidenced by elemental analyses, mass-spectrometry and ^{13}C and ^{1}H NMR data (see Section 3).



R_6=F (**1, 11**); R_6=morpholinyl (**2a, 12a**); R_6=methylpiperaziny1 (**2c, 12b**); R_6=thiomorpholinyl (**2d, 12c**); R_6=methoxy (**6a, 12d**).

Scheme 5.

The ^{1}H NMR spectra of compounds **12a–d** in $(CD_3)_2SO$ recorded at room temperature proved to be very sharp and two doublets corresponding to H-4 and H-7 protons with characteristic values of coupling constants $^{3}J_{H,F}$ and $^{4}J_{H,F}$ were observed. In particular, for compound **12a** the following coupling constants were measured: $^{3}J(H4\text{-}F5) = 12.0$ Hz, and $^{4}J(H7\text{-}F5) = 7.8$ Hz.

3. Experimental

The ^{1}H NMR spectra were recorded in $(CD_3)_2SO$ using a Bruker WM-250 (250 MHz) spectrometer. The ^{13}C NMR spectra and low temperature ^{13}C, ^{1}H and ^{19}F NMR spectra in $(CD_3)_2CO$ were obtained on a Bruker DRX-400 spectrometer (100 MHz for ^{13}C nuclei, and 400 MHz for protons and 376 MHz—for ^{19}F nuclei). All spectral data are reported

Table 2
^{1}H NMR spectral data for 5(6)-R-6(5)-R_1-substituted benzofuroxans in [$(CD_3)_2SO$] (room temperature)

Compound	R5(6), $R_1$6(5)	Chemical shifts (δ) (ppm)	
		H-4, H-7	R5(6), $R_1$6(5)
2a	F, morpholino	6.74, 7.45 (2H, br.s)	3.08 [4H, m, $N(CH_2)_2$], 3.75 [4H, m, $(CH_2)_2O$]
2b	F, pyrrolidino	6.01, 7.34 (2H, br.s)	2.04 [4H, m, $N(CH_2)_2$], 3.05 [4H, m, $(CH_2)_2$]
2c	F, 4-methylpiperazin-1-yl	6.69, 7.42 (2H, br.s)	2.31 (3H, s, NCH_3), 2.49 [4H, m, $N(CH_2)_2$], 3.17 [4H, m, $N(CH_2)_2$]
2d	F, thiomorpholino	6.72, 7.44 (2H, br.s)	2.78 [4H, m, $N(CH_2)_2$], 3.43 [4H, m, $(CH_2)_2S$]
3a	F, Methylamino	5.77, 6.13, 7.18, 7.40 (0.6:0.4:0.4:0.6, 2H, br.s)	2.81, 2.83 (3H, br.s, CH_3), 7.05 (1H, br.s, NH)
3b	F, ethylamino	5.82, 6.18, 7.15, 7.38 (1.0:0.7:0.7:1.0, 2H, br.s)	1.22 (3H, br.t, CH_3), 3.26 (2H, br.q, CH_2), 6.79 (1H, br.s, NH)
4	F, azido	7.57, 7.64 (2H, br.s)	–
5	Azido, azido	7.50 (2H, s)	–
6a	F, methoxy	7.07, 7.75 (2H, br.s)	3.99 (3H, br.s, OCH_3)
6b	F, ethoxy	7.00, 7.55 (2H, br.s)	1.46 (3H, br.t, CH_3), 4.23 (2H, br.q, CH_2)
6c	F, (2-tetrahydrofuryl)methoxy	7.00, 7.67 (2H, br.s)	1.76 (4H, br.m, $2CH_2$), 3.84 (2H, br.m, CH_2), 4.23 (3H, br.m, OCH_2)
(**7a**)	F, bornyloxy	6.91, 7.63 (2H, br.s)	0.92, 0.96, 0.99 (9H, 3s, $3CH_3$), 1.83 (6H, m, $3CH_2$), 2.07 (1H, br.s, CH), 4.56 (1H, br.s, OCH)
7b	F, *iso*-bornyloxy	6.94, 7.82 (2H, br.s)	0.79, 0.80, 0.82 (9H, 3s, $3CH_3$), 1.86 (6H, m, $3CH_2$), 2.12 (1H, br.s, CH), 4.61 (1H, br.s, OCH)
8a	Methoxy, methoxy	6.83 (2H, s)	3.95 (6H, s, $2CH_3$)
8b	Ethoxy, ethoxy	6.75 (2H, s)	1.43 (6H, t, $2CH_3$), 4.16 (4H, q, $2CH_2$)
8c	2-Hydroxyethoxy, 2-hydroxyethoxy	6.80 (2H, br.s)	3.79 (4H, m, $2OCH_2$), 4.12 (4H, m, $2CH_2$), 4.62 (2H, t, 2OH)
9a	Morpholino, methoxy	6.47, 6.94 (2H, br.s)	3.11 [4H, m, $N(CH_2)_2$], 3.76 [4H, m, $(CH_2)_2O$], 3.94 (3H, br.s, OCH_3)
9b	Pyrrolidino, methoxy	5.87, 6.81 (2H, br.s)	1.92 (4H, m, CH_2), 3.52 (4H, m, NCH_2), 3.95 (3H, br.s, OCH_3)

in ppm in the δ-scale relative to internal TMS (^{1}H and ^{13}C NMR) or hexafluorobenzene (^{19}F NMR), respectively. ^{19}F chemical shifts were measured from internal C_6F_6 and converted to the δ-scale with $CFCl_3$ as reference, using conversion relation $\delta(CFCl_3) = \delta(C_6F_6) - 162.9$ ppm. The X-ray structure **2a** was recorded using a Bruker AXS SMART 1000 with CCD detector.

Spectroscopy analytical and other data are given in Tables 1–3.

3.1. Preparation of 5,6-difluorobenzofuroxan (*1*)

2-Nitro-4,5-difluorophenylazide [13] (7.8 g; 0.04 mol) was refluxed for 1 h in acetic acid, cooled and poured into an ice-water (300 cm^3). The precipitate obtained was filtered off, dried in air and recrystallized from hexane to give 5,6-difluorobenzofuroxan (**1**). ^{1}H NMR spectral data [$(CD_3)_2SO$]: δ 7.79 (br.t, H-4, H-7).

3.2. Reaction of 5,6-difluorobenzofuroxan (*1*) with cycloalkylimines

Cycloalkylimine (0.0012 mol) was slowly added to a solution of 5,6-difluorobenzofuroxan (**1**) (0.17 g; 0.0010 mol) in ethanol (3 ml) at 20–25 °C. The reaction mixture was stirred at room temperature for 3–4 h. The precipitate obtained was filtered off and recrystallized from ethanol to give 5(6)-fluoro-6(5)-cycloalkyliminobenzofuroxan (**2a–d**).

3.3. Oxidation of 3-fluoro-4-morpholino-5-nitroaniline by KOBr

Solution of KOBr 10–15% 75 ml was added to 3-fluoro-4-mopholino-5-nitroaniline (0.48 g, 0.0020 mol) in 15 ml $HCON(CH_3)_2$ at 10–15 °C and stirred at room temperature for 5–7 min. The reaction mixture was cooled and the precipitate obtained was filtered to give 5(6)-fluoro-6(5)-morpholinobenzofuroxan (**2a**).

3.4. Reaction of 5,6-difluorobenzofuroxan (*1*) with alkylamines

5,6-Difluorobenzofuroxan (**1**) (0.17 g; 0.0010 mol) was added to a 7–10% solution of alkylamine in ethanol (3 ml) and stirred at room temperature for 1–3 h. The precipitate obtained was filtered off and recrystallized from ethanol–water to give 5(6)-fluoro-6(5)-alkylaminobenzofuroxan (**3a–b**).

3.5. Reaction of 5,6-difluorobenzofuroxan (*1*) with sodium azide

A solution of sodium azide (0.20 g; 0.0020 mol) in water (2 ml) was added to a solution of 5,6-difluorobenzofuroxan (**1**) (0.17 g: 0.0010 mol) in ethanol (10 ml). The reaction mixture was stirred at room temperature for 72 h. The precipitate obtained was filtered off, dried and recrystallized from ethanol to give 5,6-diazobenzofuroxan (**5**). The mother

Table 3
Analytical and mass-spectral data for synthesis compounds **1–12**

Compound	Melting point (°C)	Yield (%)	Elemental analysis data found (calculated) (%)			Empirical formula	Mass-spectral data EIMS 70 eV, *m/z* (relative intensity)
			C	H	N		
1	59–60	76	42.0 (41.9)	1.3 (1.2)	16.5 (16.3)	$C_6H_2F_2N_2O_2$	172 $[M]^+$ (1 0 0), 156 $[M - O]^+$ (6), 142 $[M - O\text{-}N]^+$ (3), 112 $[M - O\text{-}N\text{-}NO]^+$ (65)
2a	121–123	78	50.2 (50.3)	4.2 (4.2)	17.6 (17.7)	$C_{10}H_{10}FN_3O_3$	223 $[M]^+$ (1 0 0), 207 $[M - O]^+$ (54), 175 $[M - 48]^+$ (67)
2b	129–130	56	53.8 (53.6)	4.5 (4.3)	18.8 (18.5)	$C_{10}H_{10}FN_3O_2$	223 $[M]^+$ (1 0 0), 207 $[M - O]^+$ (54), 175 $[M - 48]^+$ (67)
2c	84–86	54	52.4 (52.5)	5.2 (5.3)	22.2 (22.5)	$C_{11}H_{13}FN_4O_2$	252 $[M]^+$ (1 0 0), 235 $[M - CH_3]^+$ (15), 210 $[M - 42]^+$ (13)
2d	134–136	67	47.1 (47.3)	4.0 (4.0)	16.5 (16.7)	$C_{10}H_{10}FN_3O_2S$	255 $[M]^+$ (1 0 0), 239 $[M - O]^+$ (13), 195 $[M - 60]^+$ (20)
3a	103–104	83	45.9 (45.7)	3.3 (3.2)	22.9 (23.1)	$C_7H_6FN_3O_2$	183 $[M]^+$ (1 0 0), 167 $[M - O]^+$ (5), 123 $[M - 60]^+$ (93)
3b	112–114	93	48.7 (48.9)	4.1 (4.1)	21.3 (21.2)	$C_8H_8FN_3O_2$	197 $[M]^+$ (93), 181 $[M - O]^+$ (7), 166 $[M - 31]^+$ (8)
4	99–101	28	36.9 (37.3)	1.0 (0.9)	35.9 (35.8)	$C_6H_2FN_5O_2$	195 $[M]^+$ (43), 167 $[M - N_2]^+$ (22), 153 $[M - 42]^+$ (2)
5	113–115	57	33.0 (33.4)	0.9 (0.8)	51.4 (51.7)	$C_6H_2N_8O_2$	218 $[M]^+$ (92), 190 $[M - N_2]^+$ (12), 153 $[M - 65]^+$ (87)
6a	96–97	83	45.8 (45.9)	2.7 (2.8)	15.2 (15.4)	$C_7H_5FN_2O_3$	184 $[M]^+$ (67), 169 $[M - 15]^+$ (24), 153 $[M - 31]^+$ (48)
6b	64–66	75	48.5 (48.3)	3.6 (3.4)	14.1 (14.4)	$C_8H_7FN_2O_3$	198 $[M]^+$ (56), 170 $[M - 28]^+$ (42), 154 $[M - 44]^+$ (29)
6c	134–135	84	52.0 (52.2)	4.4 (4.5)	11.0 (11.1)	$C_{11}H_{11}FN_2O_4$	254 $[M]^+$(23), 212 $[M - 42]^+$ (3), 170 $[M - 84]^+$ (4)
7a	98–99	36	62.7 (63.0)	6.3 (6.3)	9.2 (9.4)	$C_{16}H_{19}FN_2O_3$	306 $[M]^+$ (3), 137 $[M - C_{10}H_{17}]^+$ (68), 121 $[M - 153]^+$ (2)
7b	110–112	29	62.7 (62.7)	6.3 (5.9)	9.2 (9.2)	$C_{16}H_{19}FN_2O_3$	306 $[M]^+$ (4), 137 $[M - C_{10}H_{17}]^+$ (71), 121 $[M - 153]^+$ (5)
8a	191–193	78	49.0 (48.7)	4.1 (4.5)	14.3 (14.7)	$C_8H_8N_2O_4$	196 $[M]^+$ (93), 136 $[M - O\text{-}N\text{-}O\text{-}N]^+$ (1 0 0), 121 $[M - 75]^+$ (21)
8b	205–207	82	53.6 (53.6)	5.4 (5.0)	12.5 (12.9)	$C_{10}H_{12}N_2O_4$	224 $[M]^+$ (99), 196 $[M - 28]^+$ (15), 164 $[M - 60]^+$ (43)
8c	113–115	56	46.9 (46.5)	4.7 (4.5)	10.9 (11.0)	$C_{10}H_{12}N_2O_6$	256 $[M]^+$ (57), 212 $[M - (CH_2)_2OH]^+$ (34), 168 $[M - 90]^+$ (78)
9a	191–193	80	52.6 (52.4)	5.2 (5.2)	16.7 (16.4)	$C_{11}H_{13}N_3O_4$	251 $[M]^+$ (1 0 0), 235 $[M - O]^+$ (9), 191 $[M - 60]^+$ (48)
9b	160–162	77	56.2 (56.3)	5.6 (5.8)	17.9 (18.0)	$C_{11}H_{13}N_3O_3$	235 $[M]^+$ (1 0 0), 219 $[M - O]^+$ (15), 175 $[M - O\text{-}44]^+$ (86)
11	143–144	37	46.2 (46.0)	1.3 (1.1)	18.0 (17.8)	$C_6H_2F_2N_2$	156 $[M]^+$ (1 0 0), 135 $[M - 21]^+$ (32), 108 $[M - 48]^+$ (14)
12a	157–159	62	53.8 (53.6)	4.5 (4.4)	18.8 (19.0)	$C_{10}H_{10}FN_3O_2$	223 $[M]^+$ (1 0 0), 208 $[M - 15]^+$ (5), 165 $[M - 58]^+$ (63)
12b	161–163	58	55.9 (55.7)	5.5 (5.5)	23.7 (23.8)	$C_{11}H_{13}FN_4O$	236 $[M]^+$ (1 0 0), 194 $[M - 42]^+$ (19), 165 $[M - 71]^+$ (12)
12c	156–157	75	50.2 (50.6)	4.2 (4.0)	17.6 (17.9)	$C_{10}H_{10}FN_3OS$	239 $[M]^+$ (1 0 0), 224 $[M - 15]^+$ (8), 192 $[M - 47]^+$ (23)
12d	137–138	54	50.0 (49.8)	3.0 (3.1)	16.7 (16.6)	$C_7H_5FN_2O_2$	168 $[M]^+$ (1 0 0), 144 $[M - 24]^+$ (4), 137 $[M - 31]^+$ (18)

liquor was evaporated to dryness, the residue was recrystallized from ethanol to give 6-azido-5-fluorobenzofuroxan (**4**).

*3.6. Reaction of 5,6-difluorobenzofuroxan (**1**) with liquid alcohols in the presence of one equivalent of sodium*

5,6-Difluorobenzofuroxan (**1**) (0.17 g; 0.0010 mol) was added to a solution of sodium (0.0010 mol) in alcohol (3 ml) and the reaction mixture was stirred at room temperature for 5–15 h. The precipitate obtained was filtered off and recrystallized from ethanol to give 5(6)-fluoro-6(5)-alkoxybenzofuroxan (**6a–c**).

*3.7. Reaction of 5,6-difluorobenzofuroxan (**1**) with solid alcohols in the presence of one equivalent of sodium*

Alcohol (0.0012 mol) was added to a solution of sodium hydroxide (0.04 g; 0.0010 mol) in Me_2SO (3 ml). After addition of 5,6-difluorobenzofuroxan (**1**) (0.17 g; 0.0010 mol), the reaction mixture was stirred at room temperature for 4–8 h, and then poured into ice-water (30 ml). The precipitate obtained was filtered off, dried and recrystallized from water–ethanol to give 5(6)-fluoro-6(5)-alkoxybenzofuroxan (**7a–b**).

*3.8. Reaction of 5,6-difluorobenzofuroxan (**1**) with alcohols in the presence of two equivalents of sodium*

5,6-Difluorobenzofuroxan (**1**) (0.17 g; 0.0010 mol) was added to a solution of sodium (0.05 g; 0.0020 mol) in alcohol (3–4 ml) and the reaction mixture was stirred at room temperature for 1–10 h. The precipitate obtained was filtered off, recrystallized from methanol to give 5,6-dialkoxybenzofuroxan (**8a–c**).

*3.9. Reaction of 5(6)-fluoro-6(5)-methoxybenzofuroxan (**3a**) with cycloalkylimines*

Cycloalkylimine (0.0015 mol) was added to a solution of 5(6)-fluoro-6(5)-methoxybenzofuroxan (**3a**) (0.18 g; 0.0010 mol) in methanol (3 ml). The reaction mixture was refluxed for 1–2 h and cooled. The precipitate obtained was filtered off and recrystallized from methanol to give 6(5)-methoxy-5(6)-cycloalkyliminobenzofuroxan (**9a–b**).

*3.10. Reaction of 5(6)-fluoro-6(5)-morpholinobenzofuroxan (**2a**) with methanol in the presence of one equivalent of sodium*

5(6)-Fluoro-6(5)-morpholinobenzofuroxan (**2a**) (0.18 g; 0.0010 mol) was added to a solution of sodium (0.02 g;

0.0010 mol) in methanol (3 ml). The reaction mixture was refluxed for 1.5 h and cooled. The precipitate obtained was filtered off and recrystallized from methanol to give 5-methoxy-6-morpholinobenzofuroxan (**10**) (0.24 g, 67%). Melting point, ^{1}H NMR spectra and mass-spectrometry data of **10** proved to be identical with those of compound **9a**.

3.11. Reduction of 5,6-difluorobenzofuroxan with triphenylphosphine

5,6-Difluorobenzofuroxan (**1**) (0.17 g, 0.0010 mol) was added to a solution of triphenylphosphine (0.39 g; 0.0015 mol) in benzene (3 ml). The reaction mixture was refluxed for 1 h, cooled and evaporated to dryness. The precipitate obtained was sublimed in vacuum (80 °C, 15 mm) to give 5,6-difluorobenzofurazan (**11**). ^{1}H NMR spectral data [$(CD_3)_2SO$]: δ 8.14 (t, H-4, H-7, $J_{H,F} = 8.2$ Hz).

3.12. Reduction of 5(6)-fluoro-6(5)-R-benzofuroxan with triphenylphosphine

5(6)-Fluoro-6(5)-R-benzofuroxan (**2a**, **2c**, **2d**, **6a**) (0.0010 mol) was added to a solution of triphenylphosphine (0.39 g; 0.0015 mol) in benzene (3 ml). The reaction mixture was refluxed for 3 h, cooled and evaporated to dryness. The precipitate obtained was purified by column chromatography on silica gel using CH_2Cl_2 to give 5-fluoro-6-R-benzofurazan (**12a–d**).

12a: ^{13}C NMR spectral data [$(CD_3)_2SO$]: δ 51.78 (NCH_2, $^4J_{CF} = 4.7$ Hz, $^1J_{CH} = 137.2$ Hz), 67.02 (OCH_2, $^1J_{CH} = 143.8$ Hz), 99.70 (C-7, $^3J_{CF} = 4.0$ Hz, $^1J_{CH} = 170.4$ Hz, $^4J_{CH} = 1.5$ Hz), 100.26 (C-4, $^2J_{CF} = 28.0$ Hz, $^1J_{CH} = 173.9$ Hz, $^4J_{CH} = 1.4$ Hz), 147.31 (C-3a, $^3J_{CF} = 14.8$ Hz, $^3J_{C,H} = 6.1$ Hz, $^2J_{CH} = 1.3$ Hz), 147.72 (C-6, $^2J_{CF} = 15.8$ Hz, $^3J_{CH} = 5.9$ Hz, $^3J_{CH} = 1.0$ Hz), 148.69 (C-7a, $^4J_{CF} = 0.7$ Hz, $^3J_{CH} = 5.4$ Hz), 161.08 (C-5a, $^1J_{CF} = 262.4$ Hz, $^3J_{CH} = 9.8$ Hz, $^2J_{CH} = 6.4$ Hz). ^{1}H NMR spectral data [$(CD_3)_2SO$]: δ 3.25 [4H, m, $(CH_2)_2N$)], 3.84 [4H, m, $(CH_2)_2O$], 7.19 (1H, d, H-7, $^4J_{H,F} = 7.8$ Hz), 7.64 (1H, d, H-4, $^3J_{H,F} = 12.0$ Hz). ^{19}F NMR spectral data [$(CD_3)_2SO$]: 108.24 (dd, $^3J_{H,F} = 12.0$ Hz, $^4J_{H,F} = 7.8$ Hz).

12b: ^{1}H NMR spectral data [$(CD_3)_2SO$]: δ 2.27 (3H, s, CH_3), 2.51 [4H, m, $(CH_2)_2N$], 3.19 [4H, m, $(CH_2)_2N$], 7.15 (1H, d, H-7, $^4J_{H,F} = 7.0$ Hz), 7.69 (1H, d, H-4, $^3J_{H,F} = 12.0$ Hz).

12c: ^{1}H NMR spectral data [$(CD_3)_2SO$]: δ 2.79 [4H, m, $(CH_2)_2N$], 3.45 [4H, m, $(CH_2)_2O$], 7.23 (1H, d, H-7, $^4J_{H,F} = 8.0$ Hz), 7.66 (1H, d, H-4, $^3J_{H,F} = 12.0$ Hz).

12d: ^{1}H NMR spectral data [$(CD_3)_2SO$]: δ 4.02 (3H, s, OCH_3), 7.40 (1H, d, H-7, $^4J_{H,F} = 8.0$ Hz), 7.75 (1H, d, H-4, $^3J_{H,F} = 13.0$ Hz).

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