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Synthesis and Properties of Some New 5-Fluoro-6-(heterocyclyl) Benzofuroxans

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A series of 5-fluoro-6-(N-heterocyclyl) benzofuroxans **(3b–e)** have been prepared by hypochlorite oxidative cyclization of the respective 4-fluoro-5-(*N*-heterocyclyl)-2-nitroanilines **(2b–e)**. The heterocyclyls include piperazine, N-(2-hydroxyethyl)piperazine, morpholine and thiomorpholine. Some bio-properties and spectral data of these new derivatives are presented.

INTRODUCTION

Benzofuroxans exhibit a wide spectrum of biological activity (fungicidal or fungistatic, bactericidal, parasiticidal and insecticidal)[1, 2] for which several references were cited in the patent literature.[3, 4] Benzofuroxan itself shows a marked fungistatic potency, while 5-chlorobenzofuroxan is effective in killing bacteria on potatoes.[3] As synthons, benzofuroxans have been extensively used in the "Beirut" reaction[5] for the direct preparation of many quinoxaline- and benzimidazole-N-oxides, some of which possess high levels of antibacterial activity.[5] Facile reduction of benzofuroxans is often adopted as the most convenient route to *o*-benzoquinone dioximes.[6, 7]

Time and again, these properties stimulate interest in the search for new (substituted) benzofuroxans and their congeners. In the present work, we describe the synthesis and properties of some benzofuroxans incorporating fluorine and *N*-heterocyclyls at C-5 and C-6, respectively (**3a–e**/Scheme I). This selection is inferred from the fact that both substituents are known to enhance considerably the antibacterial potency of fluoroquinolones such as ciprofloxacin (**4**)[8, 9] and ofloxacin (**5**)[10] (Figure I).

Benzofuroxans normally undergo, in solution at room temperature, rapid dynamic equilibrium of the type **3A** ⇌ **3B** (cf. Scheme-I). This phenomenon was evidenced from ^{1}H-NMR spectral studies at low temperatures.[11, 12] Throughout this paper, when we refer to this ambiguous tautomeric mixture, we shall use the system employing the lowest numbers for substituents in alphabetical order (*i.e.*, form **3B**) regardless of the form adopted in the crystal.

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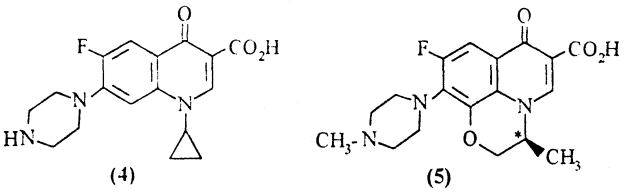

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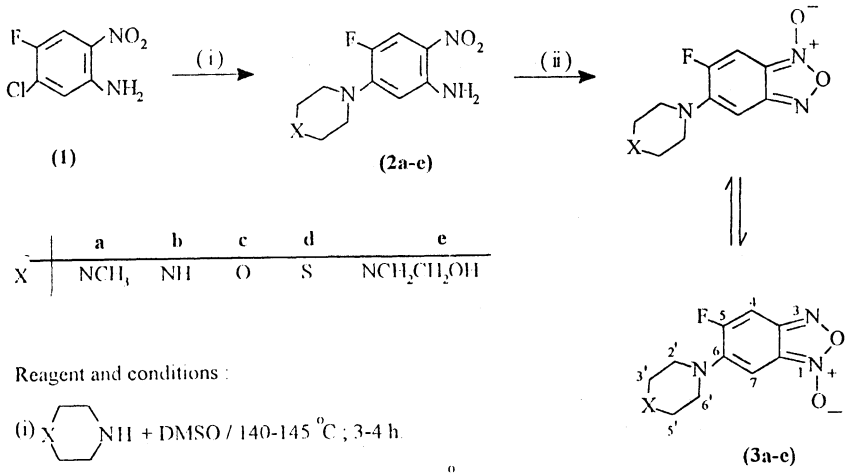
Fig. 1



Scheme-I

EXPERIMENTAL

Melting points were determined on an Electrothermal Mel. Temp. apparatus and are uncorrected. NMR spectra were recorded on a Bruker-AM 400 MHz instrument for solutions in $CDCl_3$ with TMS as internal reference. Electron impact (EI) mass spectra were obtained using a Finnigan MAT 731 spectrometer at 70 eV. Elemental analyses were carried out by M.H.W. Laboratories, Phoenix, Arizona, USA.

3-Chloro-4-fluoroaniline, morpholine, thiomorpholine and the piperazines were purchased from Acros and were used as received. 5-Chloro-4-fluoro-2-nitroaniline (**1**) was prepared from 3-chloro-4-fluoroaniline *via* N-acetylation, nitration and subsequent deacetylation according to a reported procedure.[13, 14]

Preparation of 4-fluoro-5-(heterocyclyl) nitroanilines (2b–e)

4-Fluoro-5-(N-piperazinyl)-2-nitroaniline (**2b**)**:** This compound was prepared from (**1**) and piperazine following a reported method that employs standard reaction conditions for obtaining (**2a**) and other related systems[13, 14]. Thus, a stirred solution of compound (**1**) (5.0 g; 26 mmol) and piperazine (11.2 g; 130 mmol) in DMSO (15 cm^3) was refluxed for 3–4 h at 140–145°C. The solvent was

then evaporated and the residual solid product was thoroughly washed with ice-cold water, collected by suction filtration, dried and recrystallized from $CHCl_3$/pet. ether (b.p. 40–60°C).

4-Fluoro-5-(N-morpholino)-2-nitroaniline (**2c**): This compound was prepared by the use of the same procedure described above in the preparation of **2b**, replacing piperazine with morpholine.

4-Fluoro-5-(N-thiomorpholino)-2-nitroaniline (**2d**): This compound was prepared as described above for **2b**, using thiomorpholine in place of piperazine.

4-Fluoro-5-[4′-(2-hydroxyethyl)-piperazine-1′-yl]-2-nitroaniline (**2e**): This compound was similarly prepared-from **1** and N-(2-hydroxyethyl)- piperazine.

Preparation of 5-fluoro-6-(heterocyclyl) benzofuroxans (3b–e).

5-Fluoro-6-(N-piperazinyl)benzofuroxan (**3b**): This compound is prepared by employing the following procedure which is esentially similar to that reported for the synthesis of 5-fluoro-6-(4′-methyl-1′-piperazinyl) benzofuroxan (**3a**)[13]. To a vigorously stirred solution of **2b** (4.8 g; 20 mmol) in ethanolic KOH (125 cm^3; 2.5 per cent w/v) was slowly added 7% aqueous sodium hypochlorite solution (*ca.* 30 cm^3; 28 mmol) at –2 to 3°C. The reaction mixture was further stirred for 1–2 h at the same temperature. Cold water (200 cm^3) was then added to assist precipitation of the title product (**3b**). The resulting yellow-coloured solid was then collected by suction filtration, dried and recystallized from a small volume of EtOH (cooling to –20°C). The product was further purified by recrystallization from $CHCl_3$/pet. ether (b.p. 40–60°C).

5-Fluoro-6-(N-morpholino)benzofuroxan (**3c**): This compound was prepared by hypochlorite oxidative ring closure of the respective 2-nitroaniline precursor (**2c**), following the same procedure described above for (**3b**).

5-Fluoro-6-(N-thiomorpholino)benzofuroxan (**3d**): This compound was likewise prepared *via* hypochloride oxidation of **2d**.

5-Fluoro-6-[4′-(2-hydroxyethyl)piperazin-1′-yl]benzofuroxan (**3e**): The compound was similarly prepared by treatment of **2e** with sodium hypochlorite solution.

RESULTS AND DISCUSSION

Benzofuroxans are accessible *via* oxidative cyclization of the appropriate *o*-nitroaniline precursors.[15, 16] Following this general route, the 5-fluoro-6-(*N*-heterocyclyl) derivatives (**3b–e**) were prepared by reaction of sodium hypochlorite solution with the respective 4-fluoro-5-(*N*-heterocyclyl)-2-nitroanilines (**2b–e**). The procedure is analogous to that recently described[13] for the synthesis of **3a**.

Compounds (**2b–e**) were prepared by interaction of 5-chloro-4-fluoro-2-nitroaniline (accessible from 3-chloro-4-fluoroaniline)[13, 14] with the appropriate azaheterocycle in dimethyl sulfoxide (DMSO) at 140–145°C for 3–4 h, following similar procedure reported for obtaining **2a**).[13]

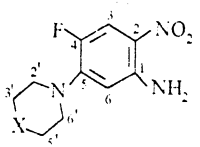
The structures of compounds **2a–e** and **3a–e** were supported by analytical (Table-1) and NMR spectral data (Tables 2–4). Electron-impact (EI) mass spectra of these compounds display the correct molecular ions in accordance with the suggested molecular formulae.

TABLE-1
CHARACTERIZATION DATA OF THE SYNTHESISED COMPOUNDS

Compd. No.	Yield (%)	m.p.* (°C)	m.f. (m.w.)	Analysis, Found (Calcd) %		
				C	H	N
2b	76	188	$C_{10}H_{13}N_4O_2F$ (240.24)	49.89 (50.00)	5.35 (5.45)	23.11 (23.32)
2c	87	172	$C_{10}H_{12}N_3O_3F$ (241.22)	49.66 (49.79)	5.11 (5.01)	17.35 (17.42)
2d	82	154	$C_{10}H_{12}N_3O_2SF$ (257.29)	46.58 (46.68)	4.83 (4.70)	16.25 (16.33)
2e	80	151	$C_{12}H_{17}N_4O_3F$ (284.29)	50.65 (50.70)	5.91 (6.03)	19.59 (19.71)
3b	64	115	$C_{10}H_{11}N_4O_2F$ (238.22)	50.30 (50.42)	4.68 (4.65)	23.45 (23.52)
3c	82	141	$C_{10}H_{10}N_3O_3F$ (239.21)	50.35 (50.21)	4.27 (4.21)	17.35 (17.57)
3d	68	210	$C_{10}H_{10}N_3O_2SF$ (255.27)	46.92 (47.05)	4.01 (3.95)	16.38 (16.46)
3e	73	134	$C_{12}H_{15}N_4O_3F$ (282.28)	50.85 (51.06)	5.39 (5.36)	19.70 (19.85)

*Compounds **2b–e** were crystallized from $CHCl_3$/pet. ether (40–60°C); compounds **3b–e** were crystallized from ethanol.

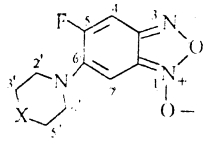
TABLE-2
PROTON MAGNETIC RESONANCE SPECTRAL DATA (δ-VALUES) OF 4-FLUORO-5-(N-HETEROCYCLYL)-2-NITROANILINES (**2a–e**) ($CDCl_3$)



Compd.	3-H (d)*	6-H (d)†	2′-H/6′-H (t)†	3′-H/5′-H (t)‡	$-NH_2$ (br. s)	X
2a	7.68	6.03	3.21	2.51	6.16	2.29 (s) CH_3—N
2b	7.78	6.04	3.21	3.02	6.08	
2c	7.77	6.03	3.84	3.97	6.04	
2d	7.73	6.05	3.50	2.74	6.09	
2e	7.78	6.05	3.27	2.68	6.08	2.65 (t) CH_2—N 3.67 (t) CH_2—O

*J_{H-F} *ca.* 13.5–14.0 Hz. †J_{H-F} *ca.* 7.5–8.0 Hz. ‡J *ca.* 4.5–5.0 Hz.

TABLE-3
PROTON MAGNETIC RESONANCE SPECTRAL DATA (δ-VALUES)* OF 5-FLUORO-6-(N-HETEROCYCLYL)BENZOFUROXANS (**3a–c** and **3e**)



Compd.	4-H (br.s)	7-H (br.s)	2′-H/6′-H (t)†	3′-H/5′-H (t)†	X
3a	7.05	6.41	3.15	2.55	2.30 (s) CH_3—N
3b	7.78	6.92	3.40	3.24	9.58 (br.s) H—N
3c	7.13	6.52	3.17	3.89	–
3e	7.09	6.50	3.21	2.71	2.65 (t) CH_2—N | 3.71 (t) CH_2—O

*NMR Solvent: $CDCl_3$ (**3a, 3c, 3e**); DMSO-d_6 (**3b**). †J *ca.* 5 Hz.

TABLE-4
CARBON-13 CHEMICAL SHIFTS (δ-VALUES)* FOR THE DIFFERENT CARBONS OF THE SYNTHESIZED COMPOUNDS (**2a-e**)

Compd	C-1	C-2 (d)†	C-3 (d)†	C-4 (d)†	C-5 (d)*	C-6 (d)	C-2′/C-6′ (d)†	C-3′/C-5′ (d)†	X
2a	143.6	123.7	112.4	146.2	147.5	103.8	49.8	54.6	45.9 (CH_3—N)
2b	145.6	122.6	111.7	145.6	147.4	105.2	48.4	43.7	
2c	143.3	124.3	112.8	146.3	147.5	103.9	49.8	66.5	
2d	143.4	124.0	112.7	146.1	147.8	104.5	52.2	27.2	
2e	143.4	125.6	112.7	146.3	147.5	104.0	49.5	57.8	52.5 CH_2—N | 59.3 CH_2—OH

*NMR solvent: $CDCl_3$ (**2a, 2c–e**); DMSO-d_6 (**2b**).
†$J_{(C,F)}$ values: C-2 (*ca.* 8.5Hz); C-3 (26.5–27 Hz); C-4 (242–255 Hz); C-5 (*ca.* 102 Hz); C_6(*ca.* 2 Hz); C-2′/C-6′ (5–5.5 Hz).

Aqueous solutions of the hydrochloride salts of the benzofuroxans (**3a–e**) were tested against a number of microorganisms. These compounds were slightly active against *Candida albicans* (MICs = 64 μg/mL for **3a, b** and 128 μg/mL for **3c, d**). Compound **3a** has an MIC of 32 μg/mL against yeast, while **3b–d** are active at MIC = 64 μg/mL. However, **3a–e** were inactive against *Aspergillus parasiticus, Fusarium oxysporum, Escherechia coli, Staphylococcus aureus and Proteus mirabilis* at concentrations ≤ 128 μg/mL.

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