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Synthesis of fluorinated furo- and pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides

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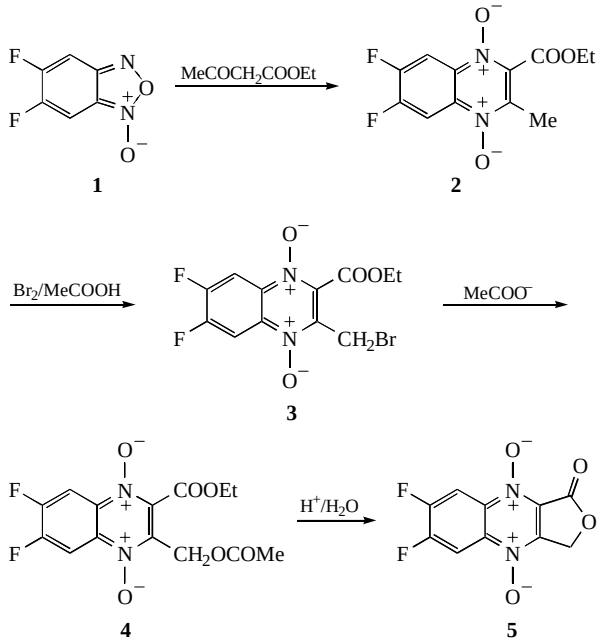
The reaction of 5,6-difluorobenzofuroxane 1 with ethyl acetoacetate in the presence of triethylamine results in the formation of 2-methyl-3-ethoxycarbonyl-6,7-difluoroquinoxaline 1,4-dioxide 2 which was converted consequently into the bromomethyl 3 and acetoxymethyl 4 derivatives; hydrolysis of the latter with hydrochloric acid gave furo[3,4-*b*]quinoxaline 4,9-dioxide 5. Compound 3 was transformed by the action of ammonia and primary alkyl amines into 2-substituted 1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides 6 and further into the corresponding 6-amino compounds 7 and 8.

Quinoxaline 1,4-dioxides and their condensed derivatives have been known to possess a variety of biological activities (see a review[1] and the references given in it). In particular, 2,3-di-(hydroxymethyl)- and 2,3-di(acetoxymethyl)-substituted quinoxaline 1,4-dioxides are known as effective antibacterials.[2] Furo[3,4-*b*]- and pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides are also of interest as biologically active compounds,[3–5] and a number of synthetic approaches to these heterocyclic systems have been reported in the literature.[2–5] However, no fluorinated derivatives of furo[3,4-*b*]- or pyrrolo[3,4-*b*]quinoxalines have hitherto been described in the literature. Meanwhile, introduction of a fluorine atom into these molecules may change their biological activity dramatically, like it does, for instance, in a series of quinolones.[6] It might also be expected that an easy nucleophilic displacement of fluorine atoms would provide a powerful synthetic tool for further functionalization of these derivatives.



Scheme 1

We report the first synthesis of fluorinated derivatives of furo[3,4-*b*]- and pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides, which is based on using 5,6-difluorobenzofuroxane **1** as the starting material and involves 2-methyl-3-ethoxycarbonyl-6,7-difluoroquinoxaline 1,4-dioxide **2** and its 2-bromomethyl derivative **3** as the key intermediates (Scheme 1).

5,6-Difluorobenzofuroxane **1** became available very recently.[7,8] It was converted into **2** by the Beirut reaction with ethyl acetoacetate in the presence of triethylamine.[9–11] We have found that 2-methyl-3-ethoxycarbonyl-6,7-difluoroquinoxaline 1,4-dioxide **2** undergoes an easy monobromination reaction on treatment with bromine in a DMF–chloroform solution or in a mixture of acetic and sulfuric acids, yielding bromomethyl derivative **3**. Nucleophilic displacement of the bromo atom in **3** gave the corresponding acetoxy compound **4** with the retention of both fluorine atoms. Acidic hydrolysis of **4** with concentrated hydrochloric acid caused a spontaneous cyclization of the intermediate hydroxymethyl derivative into lactone **5**.†

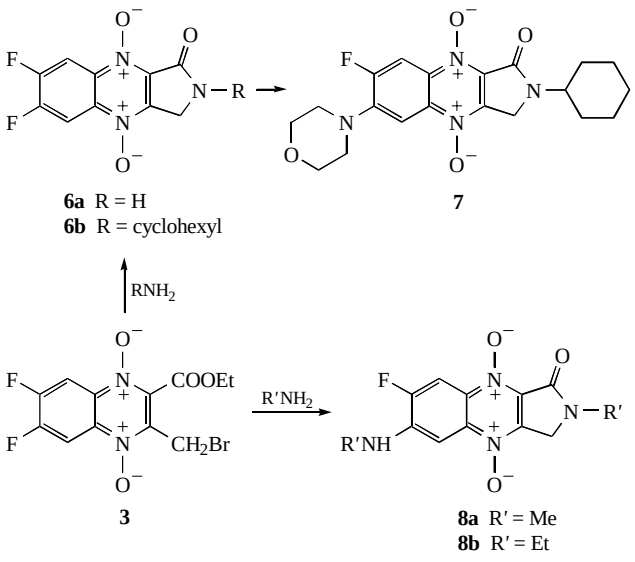
It has also been found that bromomethyl compound **3** is transformed by the action of an excess of ammonia or cyclohexylamine into the corresponding 2-substituted 6,7-difluoro-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoxaline 4,9-dioxides **6a**,**b**. The formation of the pyrrole ring in these cases is not accompanied by nucleophilic displacement of a fluoro atom in the benzene ring. This is probably due to a low solubility of compounds **6a**,**b** in acetonitrile. Indeed, when compound **3** reacts with an

† *2-Methyl-3-ethoxycarbonyl-6,7-difluoroquinoxaline 1,4-dioxide* **2**. Ethyl acetoacetate (1.6 ml, 12 mmol) was added dropwise to a suspension of 5,6-difluorobenzofuroxane **1** (1.72 g, 10 mmol) in 5 ml of triethylamine at 0–5 °C. The reaction mixture was kept under stirring first at 5 °C for 1 h and then at ambient temperature for 1 h, and cooled to 0 °C to cause precipitation of an orange oily material. Addition of 10 ml of cold water and stirring for an additional 1 h at 5–10 °C made this material solid which was filtered and recrystallised from water to give yellow crystals. Yield 1.7 g (60%), mp 111–112 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.36 (t, 3H, *Me*CH$_2$O), 2.50 (s, 3H, Me), 4.50 (q, 2H, MeC*H*$_2$O), 8.44 (dd, 1H, H-5, $^3J_{HF}$ 10.2 Hz, $^4J_{HF}$ 7.6 Hz), 8.48 (dd, 1H, H-8, $^3J_{HF}$ 10.5 Hz, $^4J_{HF}$ 7.6 Hz).

2-Bromomethyl-3-ethoxycarbonyl-6,7-difluoroquinoxaline 1,4-dioxide **3**. A solution of bromine (0.6 ml, 11.2 mmol) in 2 ml of chloroform was added dropwise to a solution of 2-methyl-3-ethoxycarbonyl-6,7-difluoroquinoxaline-1,4-dioxide **2** (2.8 g, 10 mmol) in 18 ml of DMF which was previously heated up to 80 °C. The reaction mixture was kept at 80–90 °C with stirring for 30 min, cooled to ambient temperature and poured into ice. The yellow oil formed was allowed to solidify. The solid material was collected by filtration and recrystallised from 2-propanol to give slightly yellowish crystals of **3** with mp 136–137 °C. Yield 3.3 g (92%). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.38 (t, 3H, *Me*CH$_2$O), 4.54 (q, 2H, MeC*H*$_2$O), 4.69 (s, 2H, CH$_2$Br), 8.45 (dd, 1H, H-5, $^3J_{HF}$ 9.9 Hz, $^4J_{HF}$ 7.6 Hz), 8.60 (dd, 1H, H-8, $^3J_{HF}$ 9.9 Hz, $^4J_{HF}$ 7.3 Hz).

2-Acetoxymethyl-3-ethoxycarbonyl-6,7-difluoroquinoxaline 1,4-dioxide **4**. Triethylamine (2.9 ml, 21 mmol) was added dropwise to a solution of acetic acid (1.3 ml, 21.6 mmol) in 37 ml of acetone at 20–25 °C. After 15 min compound **3** (2.0 g, 5.5 mmol) was added in portions over 10–15 min, and the reaction mixture was stirred for 1.5–2 h. The precipitate of triethylamine hydrobromide was filtered off; the filtrate was diluted with 40 ml of water and neutralized to pH 7 with an aqueous sodium bicarbonate solution. The yellow solid was recovered by filtration, washed with water and recrystallised from 60% aqueous ethanol. Yield 1.5 g (80%), mp 119–120 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.35 (t, 3H, *Me*CH$_2$O), 2.07 (s, 3H, CH$_2$OCO*Me*), 4.48 (q, 2H, MeC*H*$_2$O), 5.37 (s, 2H, C*H*$_2$OCOMe), 8.48 (dd, 1H, H-5, $^3J_{HF}$ 10.5 Hz, $^4J_{HF}$ 7.7 Hz), 8.52 (dd, 1H, H-8, $^3J_{HF}$ 10.1 Hz, $^4J_{HF}$ 7.7 Hz).

6,7-Difluoro-1-oxo-2,3-dihydrofuro[3,4-b]quinoxaline 4,9-dioxide **5**. A suspension of compound **4** (3.0 g, 9 mmol) in concentrated hydrochloric acid (14 ml) was kept at 20–25 °C for 18 h and then put into an ice bath to cool it down to 0–5 °C. A bright yellow precipitate of **5** was filtered off. The filtrate was diluted with absolute ethanol (25–30 ml) to precipitate an additional quantity of compound **5**. The combined solid of **5** was recrystallised from acetic acid, yielding 2.1 g (92%), mp 234–235 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.50 (s, 2H, CH$_2$), 8.59 (dd, 1H, H-5, $^3J_{HF}$ 10.2 Hz, $^4J_{HF}$ 7.5 Hz), 8.65 (dd, 1H, H-8, $^3J_{HF}$ 10.4 Hz, $^4J_{HF}$ 7.3 Hz).



Scheme 2

excess of methyl or ethyl amine not only closure of the pyrrole ring, but also the amino-defluorination reaction at C-6 takes place, affording compounds **8a**,**b** (Scheme 2).‡ Unequivocal evidence for the structure of **8** is provided by two-dimensional ^{1}H–^{13}C NMR spectroscopy. In the broad-band proton decoupled ^{13}C NMR of **8b** the resonance signals of C-4a and C-9a can easily be differentiated, since C-9a is coupled with F-7 ($^3J_{CF}$ = = 14.4), while the resonance signal of C-4a has no coupling. The use of the COLOC pulse sequence in the two-dimensional ^{1}H–^{13}C NMR experiment enabled us to identify a long-range coupling between C-3 protons with δ 4.55 and carbon C-4a with δ 140.67 ppm, which is in full agreement with the structure of **8b**. The fact that the fluoro atom at C-6 in fluorinated pyrrolo[3,4-*b*]quinoxalines **6** is very susceptible to a nucleophilic displacement can be used for further structural modifications of these compounds, as illustrated by the reaction of **6b** with morpholine, yielding 2-cyclohexyl-7-fluoro-6-morpholino-1-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoxaline 4,9-dioxide **7**.

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‡ *2-Cyclohexyl-6,7-difluoro-1-oxo-1,3-dihydropyrrolo[3,4-b]quinoxaline 4,9-dioxide* **6b**. Cyclohexylamine (0.3 g, 2.8 mmol) was added dropwise to a solution of compound **3** (0.5 g, 1.4 mmol) in dry acetonitrile (15 ml) with stirring. The reaction mixture was allowed to stand for 1 h; the precipitate formed was filtered off and recrystallised from acetonitrile–DMF (1:3). Yield 0.4 g (87%), mp 220–221 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.49 [m, 10H, $(CH_2)_5$], 4.00 (m, 1H, CH), 4.59 (s, 2H, CH_2), 8.55 (dd, 1H, H-5, $^3J_{HF}$ 10.2 Hz, $^4J_{HF}$ 7.4 Hz), 8.57 (dd, 1H, H-8, $^3J_{HF}$ 10.5 Hz, $^4J_{HF}$ 7.4 Hz). Compound **6a** was obtained analogously by the reaction of **3** with an excess of ammonia bubbled through the reaction mixture (see the next procedure). Yield 96%, mp 234–235 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 4.49 (s, 2H, CH_2), 8.62 (m, 2H, H-5 and H-8), 9.20 (br. s, 1H, NH).

2-Cyclohexyl-7-fluoro-6-morpholino-1-oxo-1,3-dihydro-2H-pyrrolo-[3,4-b]quinoxaline 4,9-dioxide **7**. Morpholine (0.06 ml, 0.6 mmol) was added dropwise to a suspension of compound **6b** (0.1 g, 0.3 mmol) in DMF (25 ml) with stirring. The reaction mixture, which immediately became a bright yellow solution, was allowed to stand at room temperature for 3 h; the precipitate formed was filtered off and recrystallised from ethanol. Yield 0.09 g (75%), mp 205–206 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.49 [m, 10H, $(CH_2)_5$], 3.38 [m, 4H, $N(CH_2)_2$- of morpholino], 3.80 [m, 4H, $O(CH_2)_2$- of morpholino], 4.00 (m, 1H, CH), 4.55 (s, 2H, CH_2), 7.76 (d, 1H, H-5, $^4J_{HF}$ 8.2 Hz), 8.18 (d, 1H, H-8, $^3J_{HF}$ 13.4 Hz).

2-Methyl-7-fluoro-6-methylamino-1-oxo-1,3-dihydro-2H-pyrrolo[3,4-b]-quinoxaline 4,9-dioxide **8a**. Dry methylamine (2.1 g, 68 mmol) was bubbled through a solution of compound **3** (0.6 g, 1.7 mmol) in dry acetonitrile (50 ml) at 10–15 °C for 1–1.5 h until precipitation of **8a** was completed. The precipitate was filtered off and recrystallised from acetonitrile. Yield 0.4 g (87%), mp 221–222 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 2.92 (d, 3H, NH*Me*, ^3J 4.9 Hz), 3.05 (s, 3H, N*Me*), 4.54 (s, 2H, CH_2), 7.23 (d, 1H, H-5, $^4J_{HF}$ 7.9 Hz), 7.39 (br. s, 1H, NH), 8.06 (d, 1H, H-8, $^3J_{HF}$ 11.9 Hz). Compound **8b** was obtained analogously by the reaction of **3** with an excess of ethylamine. Yield 67%, mp 223–225 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.20 (m, 6H, NCH_2*Me*, $NHCH_2$*Me*), 3.32 (m, 2H, $NHCH_2$Me), 3.53 (q, 2H, NCH_2Me), 4.55 (s, 2H, CH_2), 7.27 (d, 1H, H-5, $^4J_{HF}$ 7.9 Hz), 7.30 (br. s, 1H, NH), 8.04 (d, 1H, H-8, $^3J_{HF}$ 11.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 12.98 and 13.83 (2s, $2NCH_2$*Me*), 37.52 and 38.13 (2s, $2NCH_2$Me), 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), 140.67 (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 (s, C-1).