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TRANSFORMATIONS OF 6,7-DIFLUOROQUINOXALINE WITH INDOLES: SYNTHESIS OF INDOLE-SUBSTITUTED 6,7-DIFLUOROQUINOXALINES AND TRIS(INDOL-3-YL)METHANE DERIVATIVES

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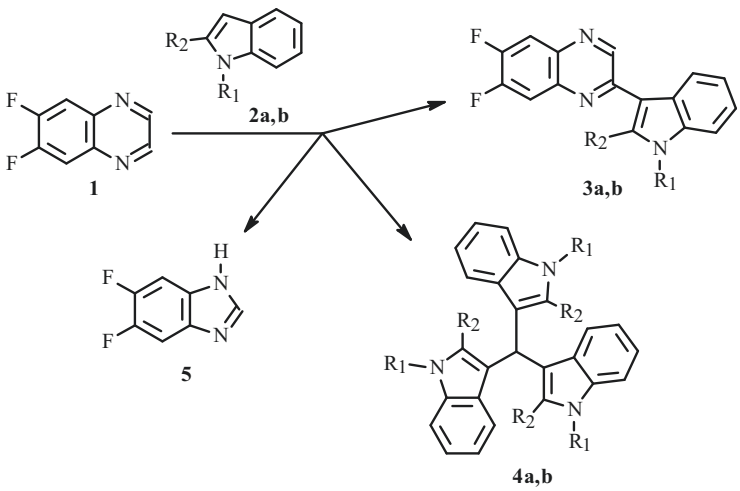
*6,7-Difluoroquinoxaline (**1**) reacted with 1- and 2-methylindoles (**2a** and **2b**) with heating in AcOH to give products from substitution of H in the heterocyclic fragment (**3a** and **3b**) and tris(indol-3-yl)methane derivatives (**4a** and **4b**).*

Keywords: 2-indolyl derivatives of 6,7-difluoroquinoxaline, tris(indol-3-yl) methanes.

Quinoxaline derivatives with various types of biological activity have been discovered [1, 2]. Quinoxaline derivatives, i.e., quinoxidine and dioxidine, are known antimicrobial agents [3]. Recently, substitution of the H in the aromatic core of 6,7-difluoroquinoxaline by several *C*-nucleophiles and of an F atom by amines were reported [4]. Indole and its derivatives are widely used as heterocyclic *C*-nucleophiles to prepare products of C–C bonding to various heterocyclic substrates [5]. The search for effective biologically active compounds among indole derivatives is promising because the indole core is the basic framework or a component part of several important natural compounds, including the amino acid tryptophan, the neuromediator serotonin, and the antibiotic turbomycin A.

In continuation of the development of efficient methods for preparing 6,7-difluoroquinoxaline derivatives using S_N^H-functionalization of C–H bonds [5], we studied the direct substitution of H in these compounds during reactions with indoles.



a: $R_1 = CH_3$, $R_2 = H$; **b:** $R_1 = H$, $R_2 = CH_3$

Scheme 1

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It was found during the work that 6,7-difluoroquinoxaline (**1**) reacted with methylindoles **2a** and **2b** with heating in AcOH to give the corresponding H-substitution products **3a** and **3b** (Scheme 1). In addition to them, the corresponding tris(indol-3-yl)methanes **4a** and **4b** were isolated from the reaction mixture in both instances. Furthermore, TLC and mass spectrometry of the reaction mixtures identified 5,6-difluorobenzimidazole **5**.

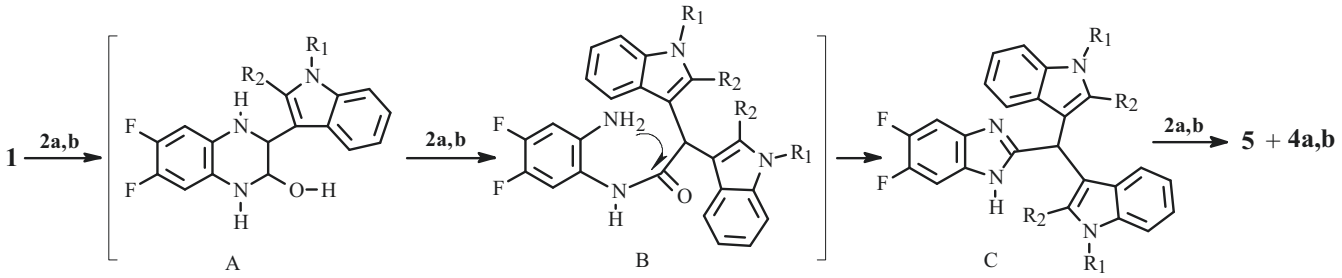
The obtained tris(indolylmethanes) **4a** and **4b** were identical to those in the literature. Compound **4a** was synthesized via condensation of 1-methyl-3-formylindole and 1-methylindole [6]; **4b** or tris(2-methylindol-3-yl)methane, from 4,6-dichloro-5-nitropyrimidine and 2-methylindole [7].

It could be proposed that the direct H-substitution to give indolylquinoxalines **3** that was described by us passed through the formation of σ-adducts. Such σ-adducts are usually oxidized using special oxidizing agents [5].

The final H-substitution products (**3**) formed during the transformations without adding special oxidants. Obviously, generated intermediates were spontaneously oxidized by atmospheric O_2.

It was shown previously that a C–C fragment was eliminated from the pyrazine core to form a tetrapyrazolylethane derivative that was easily converted to dipyrazolylmethane during the reaction of 6,7-difluoroquinoxaline with 1-phenyl-3-methylpyrazolone-5 in the presence of Et_3N [4].

Apparently, several processes were responsible for the newly observed transformation of quinoxalines. These were competitive nucleophilic addition to the quinoxaline heterocyclic core of indole and a water hydroxyl, cleavage of one C=N bond, cyclization of intermediate B, and substitution of the benzimidazole in intermediate C (Scheme 2).



a: $R_1 = CH_3$, $R_2 = H$; **b:** $R_1 = H$, $R_2 = CH_3$

Scheme 2

The quinoxaline derivatives acted in the described transformation as donors of C_1-fragments that linked three indole molecules. The remaining part of the quinoxaline molecule converted into the benzimidazole derivative, i.e., the six-membered heterocyclic fragment contracted to a five-membered one.

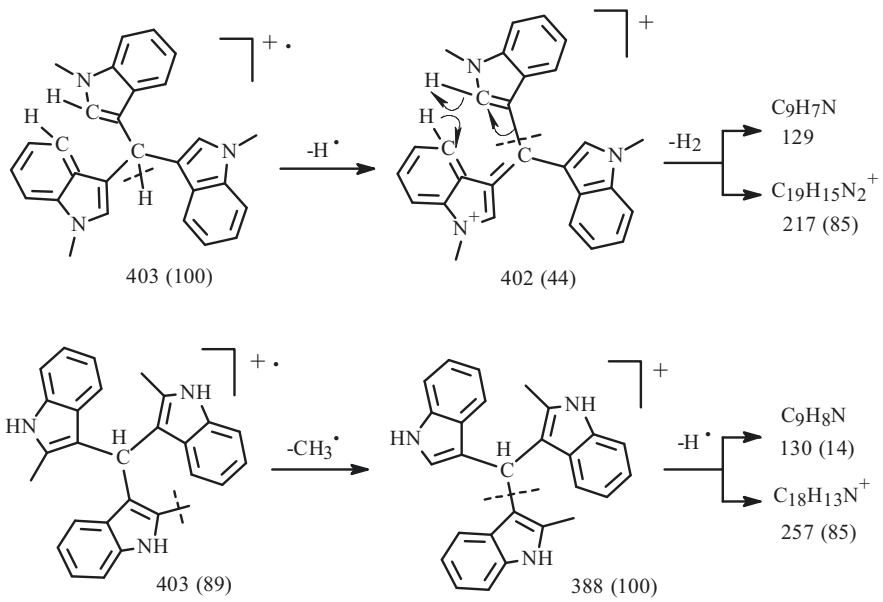
PMR spectra showed characteristic resonances for indole derivatives of difluoroquinoxalines **3** as a singlet for pyrazine H-3 at 9.2–9.4 ppm; for derivatives of tris(indol-3-yl)methanes **4**, as a singlet for the methane proton at 6.0–6.2 ppm. It is noteworthy that the chemical shifts of the methyl protons of the 2-methylindoline fragments in **3b** (2.80 ppm) and **4b** (1.92 ppm) differed significantly, probably because of deshielding by the heteroaromatic ring in **3b**.

Electron-impact (EI) mass spectra of **4a** and **4b** differed considerably. Thus, the main fragmentation pathway for **4a** was 403 (100) → 402 (44) → 271 (85) + 129 + H_2. Evidently, a hydrogen radical was initially cleaved from the molecular ion (Scheme 3). Then, the ion with *m*/*z* 402 decayed by releasing H_2 (dehydrogenation) and formed indolyl and diindolylmethane fragments through a P-process [8].

However, a similar rearrangement involving the H atoms was impossible for 2-methylindolyl derivative **4b** because the indolyl 2-position of the fragment was blocked by the methyl. The main mass spectrometric fragmentation pathway in this instance was 403 (89) → 388 (100) → 257 (85) + 130 (14) + $H^{\bullet}$. Apparently, it corresponded to initial cleavage of a methyl radical and subsequent cleavage of an ion with *m*/*z* 388 and formation of the corresponding indolyl and diindolylmethane fragments.

These characteristic mass spectrometric fragmentations of various methyl-derivatives of tris(indolylmethanes) are interesting because they are convenient and practically useful diagnostic signatures for homologs of the antibiotic turbomycin A [9].

The observed transformations of difluoroquinoxalines with indoles opens possibilities for synthesizing potentially biologically active compounds that, in turn, can act as synthons for producing new derivatives.



Scheme 3

EXPERIMENTAL

PMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded on Bruker Avance-500 and Avance-400 spectrometers. Chemical shifts of ^{1}H and ^{19}F were measured vs. internal standards of TMS and C_6F_6, respectively; of ^{13}C, vs. the solvent resonance δ_C = 39.5 ppm. EI mass spectra were taken on a Bruker Daltonics MicrOTOF-Q instrument with average ionizing potential 75 eV at 250°C.

Reaction of 6,7-Difluoroquinoxaline (1) with 1-Methylindole. Compound **1** (0.225 g, 1.35 mmol) was heated with 1-methylindole (0.5 g, 3.8 mmol) in AcOH (3 mL) at 110°C for 35 h, cooled, and stored at 20–25 for 12 h. The resulting precipitate was filtered off and recrystallized from DMF. Yield of **tris(1-methylindol-3-yl)methane (4a)**, 0.060 g (12%), mp 241–243°C [6]. The PMR spectrum was published [6]. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 404 (29), 403 (M^+, 100), 402 (44), 272 (75), 271 (85), 257 (15).

The mother liquor from crystallization was diluted with H_2O (1:1). The resulting precipitate of **6,7-difluoro-2-(1-methyl-1*H*-indol-3-yl)quinoxaline (3a)** was filtered off. Yield 0.140 g (36%), mp 155–157°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.93 (3H, s, NCH_3), 7.25 (1H, ddd, J = 7.7, 7.0, 1.0, H-5′), 7.30 (1H, ddd, J = 8.1, 7.0, 1.2, H-6′), 7.54 (1H, br.d, J = 8.1, H-7′), 7.95 (1H, dd, J = 10.9, 8.6, H-5), 8.01 (1H, dd, J = 11.4, 8.4, H-8), 8.57 (1H, s, H-2′), 8.73 (1H, br.s, J = 7.7, H-4′), 9.38 (1H, s, H-3). ^{19}F NMR spectrum (470.5 MHz, DMSO-d_6, δ, ppm, J/Hz): 26.97 (1F, ddd, J = 22.3, 10.9, 8.4, F-6), 29.85 (1F, ddd, J = 22.3, 11.4, 8.6, F-7). ^{13}C NMR spectrum (126 MHz, DMSO-d_6, δ, ppm, J/Hz): 33.00 (NCH_3), 110.10 (C-7′), 111.51 (C-3′), 114.15 (d, $^{2}J_{CF}$ = 17.3, C-8), 114.69 (dd, $^{2}J_{CF}$ = 17.2, $^{3}J_{CF}$ = 1.3, C-5), 121.01 (C-5′), 122.32 (C-4′), 122.62 (C-6′), 125.74 (C-3′a), 132.81 (C-2′), 136.19 (d, $^{3}J_{CF}$ = 9.6, C-4a), 137.54 (C-7′a), 139.28 (d, $^{3}J_{CF}$ = 10.1, C-8a), 144.38 (d, $^{5}J_{CF}$ = 2.7, C-3), 149.53 (dd, $^{1}J_{CF}$ = 250.1, $^{2}J_{CF}$ = 16.0, CF), 150.64 (d, $^{5}J_{CF}$ = 2.8, C-2), 151.17 (dd, $^{1}J_{CF}$ = 251.5, $^{2}J_{CF}$ = 15.5, CF). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 295 (M^+, 100), 267 (16), 155 (11). $C_{17}H_{11}F_2N_3$.

Reaction of 6,7-difluoroquinoxaline (1) with 2-methylindole was performed analogously. The reaction mixture was evaporated *in vacuo*. The solid was worked up with EtOH (3–4 mL). The precipitate of **tris(2-methylindol-3-yl)methane (4b)** was filtered off and rinsed with EtOH. Yield 9%, mp > 300°C (lit. [7] mp > 300°C). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.92 (9H, s, CH_3), 6.09 (1H, s, CH), 6.60 (3H, ddd, J = 7.9, 7.2, 1.0, H-5), 6.84–6.90 (6H, m, H-6, 7), 7.16 (3H, dd, J = 7.9, 1.2, H-4), 10.37 (3H, s, NH). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 404 (33), 403 (M^+, 89), 402 (22), 272 (75), 271 (15), 257 (86), 256 (32).

The EtOH mother liquor was evaporated *in vacuo*. The solid was purified by preparative chromatography using silica gel (0.040–0.063 μm, Alfa Aesar) with elution by $CHCl_3$–EtOH (30:1). Bands with R_f 0.53 (EtOH) were extracted to afford **6,7-difluoro-2-(2-methyl-1*H*-indol-3-yl)quinoxaline (3b).** Yield 25%, mp 147–148°C. ^{1}H NMR spectrum (400 MHz,

DMSO-d_6, δ, ppm, J/Hz): 2.80 (3H, s, CH_3), 7.07–7.14 (2H, m, H-5′, 6′), 7.35–7.39 (1H, m, H-7′), 7.88–7.93 (2H, m, H-5, 8), 8.12–8.16 (1H, m, H-4′), 9.21 (1H, s, H-3), 11.57 (1H, s, NH). ^{19}F NMR spectrum (376 MHz, DMSO-d_6, δ, ppm, J/Hz): 28.42 (1F, ddd, J = 21.9, 10.8, 8.6, F-6), 30.87 (1F, ddd, J = 21.9, 11.2, 8.5, F-7). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 295 (M^+, 100), 155 (41), 130 (30). $C_{17}H_{11}F_2N_3$.

Products isolated from the origin were investigated by EI MS and gave ions with *m/z* 154, 127, and 100 in a 5:2:1 intensity ratio. An analogous pattern of ions was observed in the EI MS of the known 5,6-difluorobenzimidazole [10] [EI, 70 eV, *m/z* (I_{rel}, %): 154 (M^+, 100), 127 (45), 100 (21)].

The presence of 5,6-difluorobenzimidazole in the reaction products was also confirmed by TLC using silica gel as the sorbent (0.040–0.063 μm, Alfa Aesar) and authentic 5,6-difluorobenzimidazole with elution by $CHCl_3$–EtOH (6:1), R_f 0.39.

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