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SYNTHESIS OF MORPHOLINYL AND PIPERAZINYL DERIVATIVES OF POLYFLUORODIBENZ[*b,f*]-1,4-OXAZEPINES

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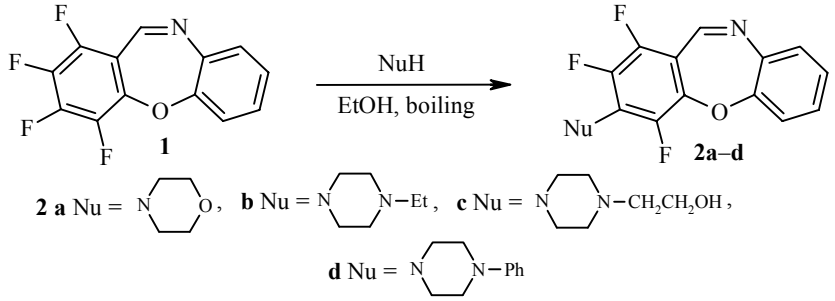
A series of polyfluoro-substituted dibenz[b,f]-1,4-oxazepines with morpholinyl-4 or 4-R-piperazinyl-1 groups in positions 3, 7, or 11 has been synthesized.

Keywords: morpholino- and 4-R-piperazino-substituted polyfluorodibenz[*b,f*]-1,4-oxazepines, nucleophilic substitution.

We previously have proposed a method for the synthesis of polyfluoro-substituted dibenz[*b,f*]-1,4-oxazepines [1] and have shown that their reactions with the simplest O- and N-nucleophiles led to substitution of fluorine atom in positions 3 or 7 by the corresponding group [2]. It is known that derivatives of dibenz[*b,f*]-1,4-oxazepine possess a variety of biological activities [3,4]. It has been shown in this example and examples of other systems that the introduction of the alicyclic amine residue, especially that of piperazine, into molecule of the physiologically active substance increases its pharmacological properties considerably [4-6]. In this connection we attempted to synthesize polyfluorodibenz[*b,f*]-1,4-oxazepines containing morpholinyl or N-R-piperazinyl residues.

In agreement with previous results [2], reaction of 1,2,3,4-tetrafluorodibenz[*b,f*]-1,4-oxazepine (**1**) with morpholine or N-R-piperazines in boiling ethanol gave the 3-amino-substituted oxazepines **2a-d**.



6,7,8,9-Tetrafluorodibenz[*b,f*]-1,4-oxazepine (3), containing the fluorine atoms in the ring bonded to the nitrogen atom, as expected [2] did not react with morpholine under these conditions. When the reaction was carried out in DMF at 100°C a mixture of two substances was formed, each of which contained three signals of equal intensity in its ^{19}F NMR spectrum. The overall character of the NMR spectrum, which contained a

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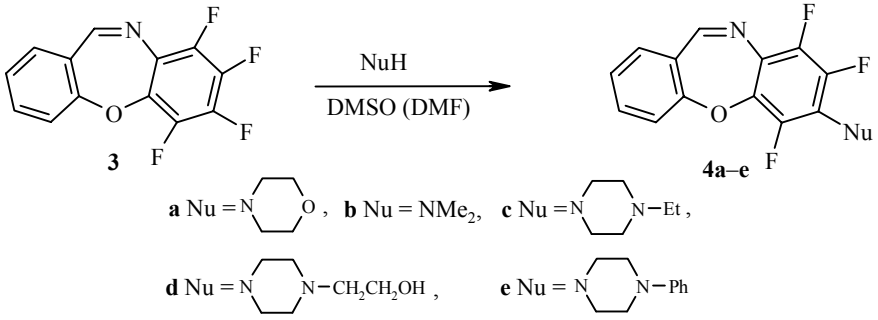
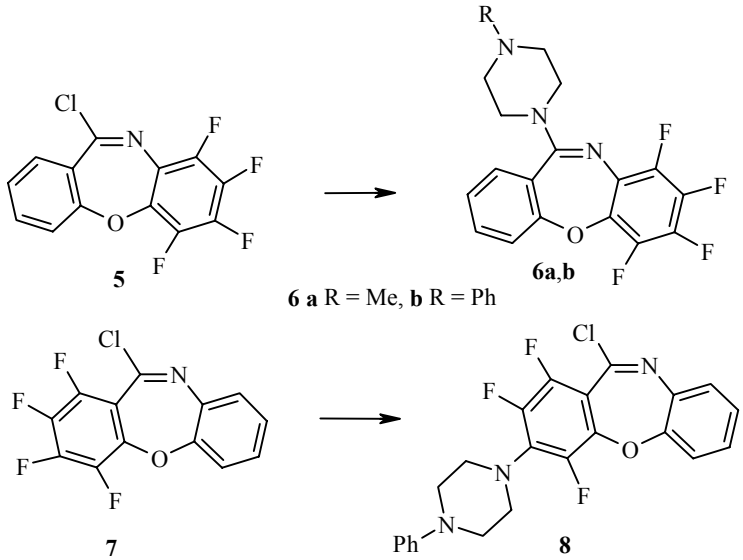
triplet at 2.92 ppm with SSCC 2 Hz, permitted to conclude that the signal of 7-morpholino-substituted oxazepine **4a** was accompanied by the formation of 7-dimethylamino-substituted oxazepine **4b**. The latter was identified by spectroscopic data with a sample obtained from compound **3** and dimethylamine in aqueous DMSO. The ability of DMF to act as a donor of dimethylamino group when nucleophilic substitution of fluorine atom was carried out in it as solvent has been noted previously [7, 8]. These results prompted us to use DMSO as solvent. When the compound **3** was heated in this with morpholine or N-R-piperazines individual 7-amino-substituted oxazepines **4a,c-e** were formed.



Derivatives of dibenz[*b*,*f*]-1,4-oxazepines with amino group at position 11 possess neuroleptic activity. For example, 2-chloro-11-(1-methylpiperazinyl-4)dibenz[*b*,*f*]-1,4-oxazepine is used medically under the name Loxapine [4].

In the current study polyfluoro-substituted analogs of the known compounds **6a** and **6b** were synthesized by the reaction of 11-chloro-6,7,8,9-tetrafluorodibenz[*b*,*f*]-1,4-oxazepine (**5**), the synthesis of which was described previously [9], with N-methyl- and N-phenylpiperazine. The reaction of the isomeric 11-chloro-1,2,3,4-tetrafluorodibenz[*b*,*f*]-1,4-oxazepine (**7**) with N-phenylpiperazine occurred with replacement of the fluorine atom at position 3, while the chlorine atom was retained.



The structures of the compounds synthesized were confirmed by data of elemental analysis and analysis of the ^{1}H and ^{19}F NMR spectra, in which the chemical shifts and the nature of the spin-spin splitting were in complete agreement with those of the corresponding piperidino-substituted polyfluorodibenz[*b*,*f*]-1,4-oxazepines described by us in previous papers [2, 9].

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	^{19}F NMR spectrum, δ, ppm (signals of equal intensity)	Yield, %
		C	H	F	N			
2a	$C_{17}H_{13}F_3N_2O_2$	61.61 / 61.07	3.97 / 3.89	17.09 / 17.06	8.39 / 8.38	102-105	10.7, 15.2, 15.8	73
2b	$C_{19}H_{18}F_3N_3O$	63.21 / 63.16	5.16 / 4.99	15.89 / 15.79	11.56 / 11.63	73-75	10.7, 15.3, 15.5	59
2c	$C_{19}H_{18}F_3N_3O_3$	61.25 / 60.47	4.99 / 4.77	15.48 / 15.12	11.18 / 11.14	108-110	10.9, 15.3, 15.7	79
2d	$C_{23}H_{18}F_3N_3O$	67.84 / 67.48	4.39 / 4.40	14.29 / 13.94	10.22 / 10.27	143-145	10.9, 15.3, 15.7	50
4a	$C_{17}H_{13}F_3N_2O_2$	61.30 / 61.07	3.86 / 3.89	17.47 / 17.07	8.42 / 8.38	126-129	10.9, 11.8, 14.3	59
4b	$C_{15}H_{11}F_3N_2O$	61.62 / 61.64	3.62 / 3.77	19.62 / 19.52	9.56 / 9.59	133-135	10.4, 11.2, 13.8	96
4c	$C_{19}H_{18}F_3N_3O$	63.27 / 63.16	4.96 / 4.99	16.22 / 15.79	11.69 / 11.63	107-109	11.0, 11.5, 14.4	69
4d	$C_{19}H_{18}F_3N_3O_2$	60.41 / 60.47	4.81 / 4.77	15.28 / 15.12	11.22 / 11.14	110-112	11.0, 11.6, 14.3	77
4e	$C_{23}H_{18}F_3N_3O$	68.11 / 67.48	3.99 / 4.40	14.28 / 13.94	10.12 / 10.27	99-101	11.2, 11.8, 14.5	76
6a	$C_{18}H_{15}F_4N_3O$	59.01 / 59.17	4.12 / 4.11	20.67 / 20.82	11.23 / 11.50	170-172	-3.90, -1.41, 1.24, 10.6	76
6b	$C_{23}H_{17}F_4N_3O$	64.67 / 64.64	3.93 / 3.98	17.81 / 17.80	9.81 / 9.84	222-224	-3.80, -1.89, 0.46, 9.38	90
8	$C_{23}H_{17}ClF_3N_3O$	61.93 / 62.24	3.60 / 3.86	13.05 / 12.84	8.92 / 9.47	137-140	12.9, 15.2, 25.9	69

EXPERIMENTAL

NMR spectra were recorded with a Bruker WP-200 SY instrument at 200 (^{1}H) and 188.2 (^{19}F) MHz in $CDCl_3$ with TMS (^{1}H) and C_6F_6 (^{19}F) as internal standards.

The compounds synthesized were purified by column chromatography on SiO_2 (140-315 μm). Characteristics of the compounds synthesized are given in Table 1.

1,2,4-Trifluoro-3-(morpholinyl-4)dibenz[*b,f*]-1,4-oxazepine (2a). Solution of oxazepine **1** (1.07 g, 4 mmol) and morpholine (0.71 ml, 10 mmol) in ethanol (50 ml) was boiled for 2 h, the reaction mixture was evaporated. and the residue was treated with 10% hydrochloric acid. The residue was filtered, washed with water, dried, chromatographed on a silica column with benzene, and recrystallized from heptane.

3-(1-Ethylpiperazinyl-4)-1,2,4-trifluorodibenz[*b,f*]-1,4-oxazepine (2b) was synthesized from compound **1** and N-ethylpiperazine analogously to compound **2a**. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with water, dried over $CaCl_2$, and evaporated. The residue was dissolved in chloroform and passed through a silica column. The product isolated was recrystallized from petroleum ether (b.p. 70-100°C).

1,2,4-Trifluoro-3-[1-(2-hydroxyethyl)piperazinyl-4]dibenz[*b,f*]-1,4-oxazepine (2c) was obtained analogously from oxazepine **1** and 2-hydroxethylpiperazine. The reaction mixture was evaporated, the sticky mixture triturated with hexane, dissolved in benzene, and passed through a small (10 cm) layer of silica. The product was eluted with acetone and recrystallized from petroleum ether.

1,2,4-Trifluoro-3-(1-phenylpiperazinyl-4)dibenz[*b,f*]-1,4-oxazepine (2d) was synthesized analogously from compound **1** and N-phenylpiperazine. The reaction mixture was cooled, the precipitate filtered off and recrystallized from ethanol.

The Reaction of 6,7,8,9-Tetrafluorodibenz[*b,f*]-1,4-oxazepine (3) with Morpholine. A. Solution of compound **3** (1.07 g, 4 mmol) and morpholine (0.93 ml, 12 mmol) in DMF (5 ml) was kept at 100-110°C for 6 h, then cooled and poured into water. The formed precipitate was filtered off, washed with water, dried, and chromatographed on a silica column with chloroform as eluent to give a mixture of compounds **4a** and **4b** (1.10 g). ^{1}H NMR spectrum, δ, ppm: 2.92 (t, CH_3); 3.23 (m, $2CH_2$); 3.78 (m, $2CH_2$); 7.19-7.47 (m, H_{arom}); 8.49 (s, CH=N); 8.56 (s, CH=N). ^{19}F NMR spectrum: 10.4 (d), 10.9 (d), 11.2 (dd), 11.8 (dd), 13.8 (m), 14.3 (d).

B. Oxazepine **3** (1.07 h, 4 mmol) and morpholine (0.71 ml, 10 mmol) in DMSO (10 ml) were kept at 100°C for 3 h. The reaction mixture was worked up as in method **A**. 6,8,9-Trifluoro-7-(morpholinyl-4)dibenz[*b,f*]-1,4-oxazepine **4a** was isolated by chromatography on a silica column with chloroform as eluent and was recrystallized from a heptane-benzene mixture.

7-(1-Ethylpiperazinyl-4)-, 7-[1-(2-hydroxyethyl)piperazinyl-4) and 7-(1-phenylpiperazinyl-4)-6,8,9-trifluorodibenz[*b,f*]-1,4-oxazepines (4c-e) were prepared analogously to the compound **4a**. The products were isolated by chromatography on a SiO_2 column with acetone as eluent and were recrystallized from methanol.

6,7,8,9-Tetrafluoro-11-(1-methylpiperazinyl-4)dibenz[*b,f*]-1,4-oxazepine (6a). Solution of compound **5** (0.45 g, 1.5 mmol) and N-methylpiperazine (0.3 ml, 3 mmol) in ethanol (20 ml) was boiled for 2 h. The reaction mixture was evaporated, the residue was washed with water, dried, and recrystallized from ethanol.

6,7,8,9-Tetrafluoro-11-(1-phenylpiperazinyl-4)dibenz[*b,f*]-1,4-oxazepine (6b) was synthesized analogously to compound **6a**. The precipitate which separated from the cooled reaction mixture was filtered, washed with ethanol, and recrystallized from benzene.

11-Chloro-1,2,4-trifluoro-3-(1-phenylpiperazinyl-4)dibenz[*b,f*]-1,4-oxazepine (8). Oxazepine **7** (0.90 g, 3 mmol) and N-phenylpiperazine (1.38 ml, 9 mmol) in ethanol (100 ml) was boiled for 1 h. The reaction mixture was evaporated, the residue was treated with water, dried, dissolved in benzene and chromatographed on a SiO_2 column, and the isolated product was recrystallized from a benzene-methanol mixture.

6,8,9-Trifluoro-7-dimethylaminodibenz[*b,f*]-1,4-oxazepine (4b). Solution of compound **3** (0.80 g) and 33% aqueous dimethylamine (2ml) in DMSO (5 ml) was kept at 120°C for 1 h in a sealed ampoule. The reaction mixture was poured into water, the viscous precipitate was filtered off after it had solidified, then washed with water and allowed to dry in the air. Then it was dissolved in chloroform, passed through a silica column, the chloroform was evaporated, and the residue was recrystallized from ethanol.

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