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# Synthesis of Benzothiazine Sulfonamides via Heteroatomic Diels–Alder Reaction of *para*-Fluoro-*N*-sulfinylaniline with Bicyclo[2.2.1]heptenes

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**Abstract**—Reaction of 4-fluoro-*N*-sulfinylaniline with norbornene and norbornadiene has afforded the Diels–Alder adducts of benzothiazine structure that have been oxidized into the corresponding benzothiazine sulfonamides. Structure of the obtained compounds and stereochemistry of the diene addition and epoxidation of norbornene olefin bonds have established by means of X-ray diffraction method.

**Keywords:** Diels–Alder reaction, fluoro-*N*-sulfinylaniline, sulfonamides, bicyclo[2.2.1]heptene

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Sulfonamide fragment is probably the most important of the known pharmacophore groups [1], whereas the fluorine-containing drugs such as fludrocortisone [2] and fluorouracil [3] were discovered and put into practice only in the second half of the XXth century. However, by the beginning of this century, various fluorine-containing compounds have taken firmly the niche in the pharmaceutical chemistry [4], since the fluoroaliphatic or fluoroaromatic fragments in combination with other pharmacophore groups substantially improve the medical and biological properties of key drugs. For example, introduction of the fluorine-containing substituent at the indole heterocycle of antitumor drug vinblastine molecule has increased the activity by 30 times [5].

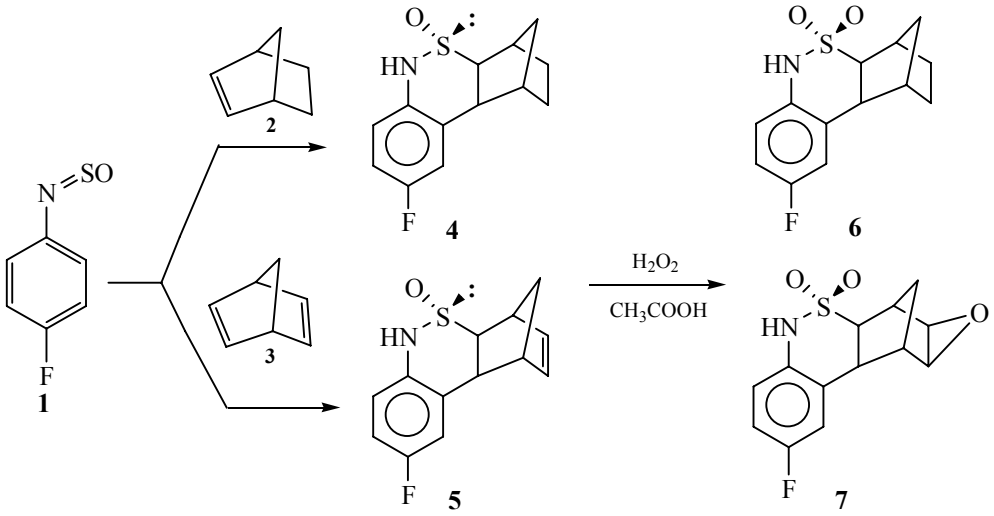
In the present study, we attempted the synthesis of fluorinated sulfonamides according to the earlier developed method [6, 7] based on the heteroatomic Diels–Alder reaction of 4-fluoro-*N*-sulfinylaniline **1** with bicyclo[2.2.1]heptenes such as norbornene **2** and norbornadiene **3**. A special feature of this Diels–Alder reaction is the use of *N*-sulfinylaniline as the diene, reacting only with the strained cycloolefine dienophiles.

The Diels–Alder reaction was conducted by heating the reactants at the diene : dienophile ratio of 1 : 1.5 in a sealed ampoule at 90–95°C during 8–10 hours. The target reaction products were *o*-benzothiazine sulfinamides **4** and **5** (70–80%). Oxidation of the adducts **4** and **5** with excess of hydrogen peroxide in an acetic acid medium at room temperature during 1 day resulted in the formation of sulfonamides **6** and **7** with yield of 50–60% (Scheme 1).

The structure of the prepared compounds was confirmed by means of IR and NMR spectroscopy. For example, IR spectra of benzo-*ortho*-thiazine sulfinamides **4** and **5** contained strong absorption bands due to stretching of S=O (1050–1060 $cm^{-1}$) and NH (3230–3260 $cm^{-1}$) groups. IR spectra of benzo-*ortho*-thiazine sulfonamides **6** and **7** contained a pair of strong absorption bands characteristic of sulfone group (1130–1135 and 1310–1320 $cm^{-1}$) and a broadened absorption band of the amide N–H bond (3200–3260 $cm^{-1}$). The spectra of all the resulting compounds contained absorption bands due to $C_{Ar}$–F stretching in the range of 1500–1505 $cm^{-1}$.

$^1$H NMR spectra of adducts **4** and **5** contained the signals of aromatic ring protons at 6.80–7.20 ppm with

**Scheme 1.**




the corresponding spin-spin coupling constants $^3J_{HH}$, $^4J_{HH}$, $^3J_{HF}$, and $^4J_{HF}$. The signals of $H^{4a}$ and $H^{10b}$ atoms were observed as the AB system with $^3J_{HH}$ = 8.7 Hz. $H^1$ and $H^4$ atoms were assigned to the broadened singlets at 2.20 and 2.35 ppm (**4**) or 2.85 and 3.07 ppm (**5**). The signals of methylene bridge protons at $C^{11}$ atom were observed as the AB system with $^2J_{HH}$ = 10.0 (**4**) and 8.8 Hz (**5**). Multiplets at 1.60 (**4**) and 6.35 ppm (**5**) corresponded to the protons of $C^2$–$C^3$ bridge. The NH protons resonated as singlets at 8.9–9.2 ppm.

$^{19}$F NMR spectra of the adducts **4** and **5** contained the signals of fluorine atom at –121.28 (**4**) and –121.19 ppm (**5**) with the corresponding constants ($^3J_{FH}$ = and $^4J_{FH}$) of spin-spin coupling with aromatic protons.

Structure of sulfinamide **4** was additionally confirmed by X-ray diffraction data (Fig. 1); the addition of 4-fluoro-*N*-sulfinylaniline occurs from the side of *endo*-methylene bridge of the bicyclic system.

$^1$H NMR spectrum of the sulfonamide **6** was essentially similar to the spectrum of the corresponding sulfinamide **4**, the only difference being that the signals of the protons of the bicyclic moiety were shifted downfield to 0.2–0.3 ppm, and the downfield shift of the NH proton signal was of 0.8 ppm.

The positions of the aromatic ring signals in the $^1$H NMR spectrum of sulfonamide **7** were similar to those for starting sulfinylamide **5**, whereas the signals of $H^{4a}$ and $H^{10b}$ were shifted downfield by 0.7 and 0.5 ppm, respectively. The $H^1$ and $H^4$ signals were shifted

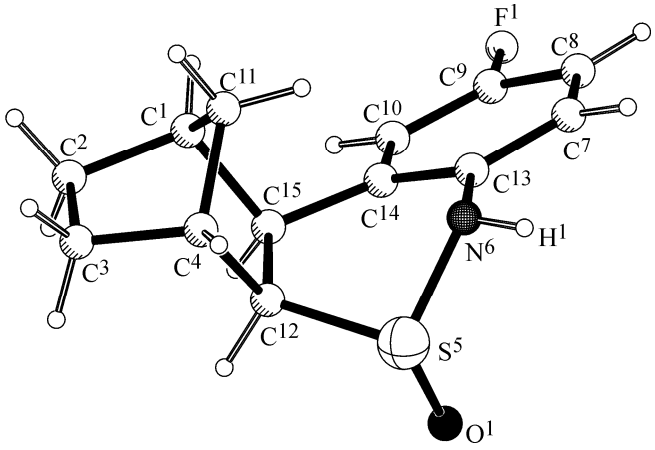



**Fig. 1.** Crystal structure of compound **4**.

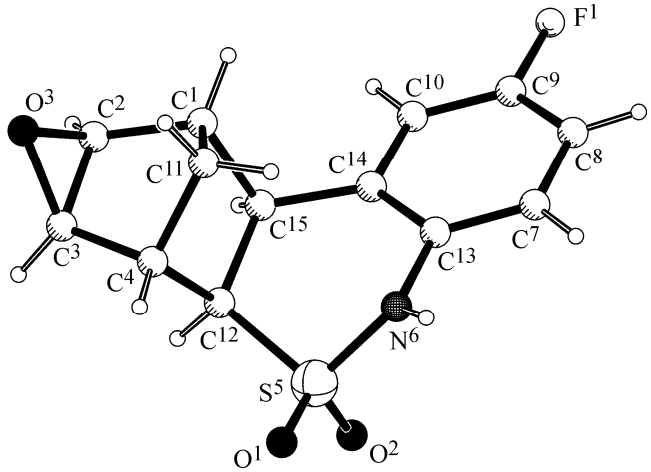



**Fig. 2.** Crystal structure of compound **7**.

towards strong-field region by 0.2 ppm. In addition, the signals of the protons of the methylene bridge at the $C^{11}$ atom were shifted downfield (by 0.1 and 0.4 ppm). Noteworthily, the spectrum of compound **7** as compared to that of compound **5** revealed the disappearance of the signals of the olefin protons, and the signals of the epoxide moiety appeared as the AB system at 3.38–3.44 ppm with spin-spin coupling constants of 3.1–3.2 Hz. The given signal assignment was made basing on the similar oxidation pathway observed earlier [7].

The fluorine atoms of sulfonamides **6** and **7** resonated as multiplet signals at –119.07 and –118.64 ppm, respectively.

The structure of sulfonamide **7** was additionally confirmed by X-ray diffraction method (Fig. 2). Both the Diels–Alder addition and the formation of epoxide ring took place on the side of *endo*-methylene bridge of the bicyclo[2.2.1]heptene fragment.

In summary, the possibility of preparation of fluorinated benzothiazine sulfonamides via the heteroatomic Diels–Alder reaction of *N*-sulfinylanilines with bicyclo[2.2.1]heptenes followed by oxidation of the resulting adducts. According to X-ray diffraction data, both the Diels–Alder reaction and the formation of the epoxide ring occurred on the side of *endo*-methylene bridge of bicyclo[2.2.1]heptene moiety.

## EXPERIMENTAL

Elemental analysis was performed using a EuroEA 3000 CHNS-analyzer. IR spectra were recorded using a Bruker Vertex 70 IR Fourier spectrometer (KBr pellets). $^1$H (400.0 MHz) and $^{19}$F (376.5 MHz) NMR spectra of the DMSO-$d_6$ solutions were registered using a Bruker Avance-400 spectrometer. Melting points were measured using a Digital Mel-Temp 3.0 analyzer.

X-Ray diffraction analysis was performed using a Bruker SMART Apex II diffractometer (graphite monochromator, Mo$K_\alpha$ irradiation, $\lambda$ = 0.71073 Å) at 293 K. The semi-empirical absorption accounting was made using SADABS software [8]. The structure was solved by the direct method using SHELXS software [9]. Non-hydrogen atoms were refined in isotropic and then anisotropic approximation for SHELXL-97 software [9]. The hydrogen atoms were placed into the calculated positions and refined in the *rider* model. Amino hydrogen atom was detected from the differential Fourier series and refined in isotropic approximation in the both structures. All the calculations were performed using WinGX [10] and AREX2 [11] software packages.

The crystals of compound **4** were rhombic, $C_{13}H_{14}FNOS$; unit cell parameters at 20°C: $a$ = 5.581(5), $b$ = 8.218(7), $c$ = 25.56 (2) Å, $V$ = 1172(2) Å$^3$, $Z$ = 4, $d_{calc}$ = 1.424 g cm$^{-3}$, space group $P2_12_12_1$, $\mu$ = 2.71 cm$^{-1}$. Intensity of 10467 reflections were measured (2337 with $I \geq 2\sigma$). The final values of the divergence factors: $R$ = 0.0425, $R_W$ = 0.0938.

The crystals of compound **7** were monoclinic, $C_{13}H_{12}FNO_3S$; unit cell parameters at 20°C: $a$ = 13.338(8), $b$ = 10.473(6), $c$ = 8.887(5) Å, $\beta$ = 105.638(7)°, $V$ = 1195(2) Å$^3$, $Z$ = 4, $d_{calc}$ = 1.563 g cm$^{-3}$, space group $P2_1/c$, $\mu$ = 2.87 cm$^{-1}$. Intensity of 9233 reflections were measured (1940 with $I \geq 2\sigma$). The final values of divergence factors: $R$ = 0.0501, $R_W$ = 0.1332.

Coordinates, refinement details, and structure factors were deposited at the Cambridge Crystallographic Data Centre (CCDC 1406833 and 1406834).

4-Fluoro-*N*-sulfinylaniline **1** was prepared via reaction of 4-fluoroaniline with the equimolar amount of $SOCl_2$ in refluxing benzene according to [7]; bp 95–96°C (12 mmHg).

**9-Fluoro-1,2,3,4,4a,10b-hexahydro-1,4-methano-6*H*-dibenzo[*c*,*e*]-5,6-thiazine-5-oxide (4).** A mixture of 15.7 g (0.1 mol) of aniline **1** and 14.1 g (0.15 mol) of norbornene **2** was heated in a sealed tube at 90–95°C during 8 h. After cooling, the reaction mixture was diluted with petroleum ether (100 mL) and filtered. The crystalline precipitate was washed with petroleum ether and recrystallized from ethanol. Yield 20.1 g (80%), mp 217–219°C. IR spectrum, ν, cm$^{-1}$: 1055 vs (S=O), 1502 s (C–F), 3258 s (N–H). $^1$H NMR spectrum, δ, ppm: 0.98 d ($1H^{11}$, $^2J_{HH}$ 10.0 Hz), 1.47 d ($1H^{11}$, $^2J_{HH}$ = 10.0 Hz), 1.60 m ($4H^{2,3}$), 2.21 s [$1H^{1(4)}$], 2.32 s [$1H^{4(1)}$], 2.98 d [$1H^{4a(10b)}$, $^3J_{HH}$ = 8.6 Hz], 3.25 d [$1H^{10b(4a)}$, $^3J_{HH}$ = 8.6 Hz], 6.82 d.d ($1H^7$, $^3J_{HH}$ = 8.6, $^4J_{HF}$ = 5.2 Hz), 6.96 t.d ($1H^8$, $^3J_{HH}$ = 8.6, $^3J_{HF}$ = 8.6, $^4J_{HH}$ = 2.8 Hz), 7.08 d.d ($1H^{10}$, $^3J_{HF}$ = 9.6, $^4J_{HH}$ = 2.8 Hz), 8.80 s (1H, NH). $^{19}$F NMR spectrum, $\delta_F$, ppm: –121.28 t.d (1F, $^3J_{FH}$ = 9.6, $^3J_{FH}$ = 8.6, $^4J_{FH}$ = 5.2 Hz). Found, %: C 62.02, 62.10; H 5.63, 5.66; N 5.43, 5.60; S 12.68, 12.80. $C_{13}H_{14}FNOS$. Calculated, %: C 62.13; H 5.61; N 5.57; S 12.76.

**9-Fluoro-1,4,4a,10b-tetrahydro-1,4-methano-6*H*-dibenzo[*c*,*e*]-5,6-thiazine-5-oxide (5)** was prepared

similarly from 15.7 g (0.1 mol) of aniline **1** and 13 g (0.15 mol) of norbornadiene **3**; the reaction duration was 10 h. After cooling, the reaction mixture was diluted with hexane (100 mL) and filtered. The crystalline precipitate was washed with cold hexane and recrystallized from ethanol. Yield 19.2 g (77%), mp 213–214°C. IR spectrum, ν, $cm^{-1}$: 1057 vs (S=O), 1504 s (C–F), 3232 s (N–H). $^1H$ NMR spectrum, δ, ppm: 1.17 d ($1H^{11}$, $^2J_{HH}$ = 8.8 Hz), 1.78 d ($1H^{11}$, $^2J_{HH}$ = 8.8 Hz), 2.76 d [$1H^{4a(10b)}$, $^3J_{HH}$ = 8.7 Hz], 2.83 s [$1H^{1(4)}$], 3.07 s [$1H^{4(1)}$], 3.10 d [$1H^{10b(4a)}$, $^3J_{HH}$ = 8.7 Hz], 6.36 m ($2H^{2,3}$), 6.87 d.d ($1H^7$, $^3J_{HH}$ = 8.7, $^4J_{HF}$ = 5.2 Hz), 6.98 t.d ($1H^8$, $^3J_{HH}$ = $^3J_{HF}$ = 8.5, $^4J_{HH}$ = 2.8 Hz), 7.16 d.d ($1H^{10}$, $^3J_{HF}$ = 9.6, $^4J_{HH}$ = 2.8 Hz), 9.15 s (1H, NH). $^{19}F$ NMR spectrum, $\delta_F$, ppm: –121.20 t.d (1F, $^3J_{FH}$ = 9.5, $^3J_{FH}$ = 8.5, $^4J_{FH}$ = 5.2 Hz). Found, %: C 62.58, 62.70; H 4.73, 4.78; N 5.50, 5.58; S 12.80, 12.92. $C_{13}H_{12}FNOS$. Calculated, %: C 62.63; H 4.85; N 5.62; S 12.86.

**9-Fluoro-1,2,3,4,4a,10b-hexahydro-1,4-methano-6*H*-dibenzo[*c*,*e*]-5,6-thiazine-5,5-dioxide (6).** 5.0 g (0.02 mol) of compound **4** was dissolved in a minimum amount of warm (≈50°C) glacial acetic acid upon stirring. After dissolution, the heating was stopped and 15 mL of 30% $H_2O_2$ was added to the mixture. The reaction mixture was incubated at room temperature during 1 day. The precipitate was separated by decantation and recrystallized from ethanol. Yield 3.4 g (64%), mp 159°C. IR spectrum, ν, $cm^{-1}$: 1134 vs and 1318 s ($SO_2$), 1502 s (C–F), 3199 vs (NH). $^1H$ NMR spectrum, δ, ppm: 1.16 d ($1H^{11}$, $^2J_{HH}$ = 10.3 Hz), 1.40–1.55 m ($4H^{2,3}$), 1.78 d ($1H^{11}$, $^2J_{HH}$ = 10.3 Hz), 2.35 s [$1H^{1(4)}$)], 2.79 s [$1H^{4(1)}$], 3.34 s [$1H^{4a(10b)}$], 3.45 s [$1H^{10b(4a)}$], 6.82 d.d ($1H^7$, $^3J_{HH}$ = 8.7, $^4J_{HF}$ = 5.3 Hz), 6.98 t.d ($1H^8$, $^3J_{HH}$ = $^3J_{HF}$ = 8.7, $^4J_{HH}$ = 2.8 Hz), 7.17 d.d ($1H^{10}$, $^3J_{HF}$ = 9.7, $^4J_{HH}$ = 2.8 Hz), 9.85 s (1H, NH). $^{19}F$ NMR spectrum, $\delta_F$, ppm: –119 t.d (1F, $^3J_{FH}$ = 9.7, $^3J_{FH}$ = 8.7, $^4J_{FH}$ = 5.3 Hz). Found, %: C 58.38, 58.50; H 5.12, 5.18; N 5.29, 5.32; S 12.03, 12.06. $C_{13}H_{14}FNO_2S$. Calculated, %: C 58.41; H 5.28; N 5.24; S 12.00.

**9-Fluoro-1,2,3,4,4a,10b-hexahydro-2,3-epoxy-1,4-methano-6*H*-dibenzo[*c*,*e*]-5,6-thiazine-5,5-dioxide (7)** was prepared similarly from 5.0 g (0.02 mol) of adduct **5**. Yield 3.5 g (62%), mp 228–229°C. IR spectrum, ν, $cm^{-1}$: 1135 vs and 1311 s ($SO_2$), 1503 s (C–F), 3263 vs (N–H). $^1H$ NMR spectrum, δ, ppm: 1.09 d ($1H^{11}$, $^2J_{HH}$ = 10.7 Hz), 1.37 d ($1H^{11}$, $^2J_{HH}$ = 10.7 Hz), 2.65 s [$1H^{1(4)}$), 2.90 s ($1H^{4(1)}$], 3.38 d [$1H^{2(3)}$, $^3J_{HH}$ = 3.2 Hz], 3.44 d [$1H^{3(2)}$, $^3J_{HH}$ = 3.2 Hz], 3.49 d [$1H^{4a(10b)}$, $^3J_{HH}$ = 9.2 Hz], 3.57 d [$1H^{10b(4a)}$, $^3J_{HH}$ = 9.2 Hz], 6.87 d.d ($1H^7$, $^3J_{HH}$ = 8.6, $^4J_{HF}$ = 5.2 Hz), 7.04 t.d ($1H^8$, $^3J_{HH}$ = $^3J_{HF}$ = 8.6, $^4J_{HH}$ = 2.8 Hz), 7.23 d.d ($1H^{10}$, $^3J_{HF}$ = 9.7, $^4J_{HH}$ = 2.8 Hz), 10.00 (1H, NH). $^{19}F$ NMR spectrum, $\delta_F$, ppm: –118.64 d. t (1F, $^3J_{FH}$ = 9.7, $^3J_{FH}$ = 8.6, $^4J_{FH}$ = 5.2 Hz). Found, %: C 5.46, 5.53; H 4.26, 4.28; N 5.05, 5.08; S 11.32, 11.36. $C_{13}H_{12}FNO_3S$. Calculated, % : C 55.51; H 4.30; N 4.98; S 11.40.

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