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Synthesis of bicyclic systems containing fused sulfolane and isoxazolidine rings

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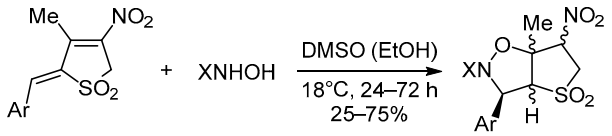


X = H, Me; Ar = Ph, 4-BrC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, furan-2-yl

A method was developed based on reactions of 2-benzylidene-3-methyl-4-nitro-3-thiolene 1,1-dioxide and its substituted analogs with hydroxylamine and *N*-methylhydroxylamine for the synthesis of 3-aryl-6a-methyl-6-nitrohexahydrothieno[2,3-*d*]isoxazole 4,4-dioxides – new representatives of original bicyclic structures combining condensed isoxazolidine and sulfolane rings. The structures of the obtained compounds were established by methods of IR spectroscopy, one-dimensional ^{1}H and ^{13}C NMR spectroscopy, two-dimensional ^{1}H–^{13}C HMQC and ^{1}H–^{13}C HMBC experiments, and X-ray structural analysis.

Keywords: bicyclic compounds, hydroxylamine, isoxazolidines, nitrosulfodienes, sulfolanes, heterocyclization, nucleophilic addition.

Thiolene and thiolane 1,1-dioxides are convenient precursors for the preparation of practically valuable compounds,[1–5] including polycyclic sulfolane-containing systems, some of which have been characterized as histamine receptor blockers,[6] have shown neuroleptic, sedative, analgesic, and anticonvulsant activity[7,8] and can inhibit the neuraminidase of influenza virus.[1,9]

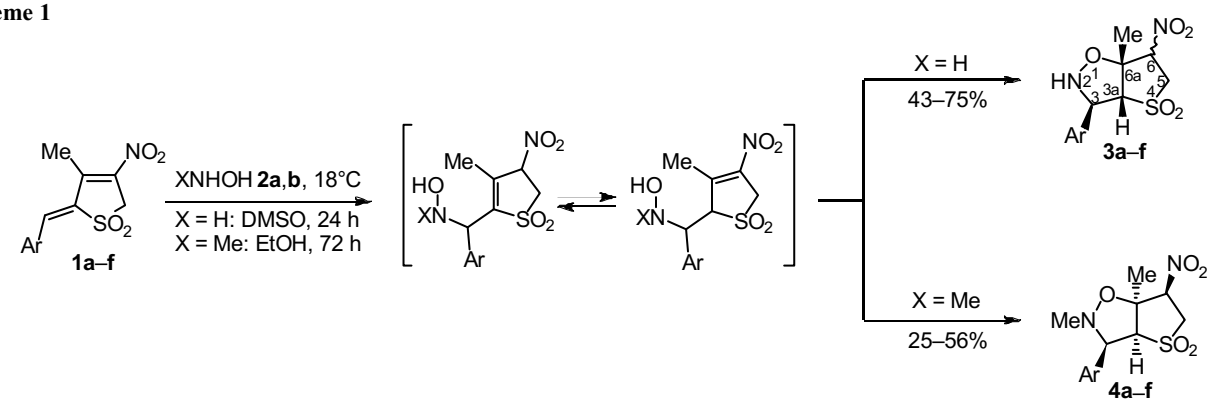
Convenient substrates for the construction of sulfolane- and sulfolene-containing polycyclic structures include *s-trans*-nitrosulfodienes of thiolene 1,1-dioxide series – 2-benzylidene-3-methyl-4-nitro-3-thiolene 1,1-dioxides **1a**–**f**, which are capable of rapid reactions with binucleophiles.[10–13] Thus, the reactions with cyclic β-diketones (dimedone, dihydroresorcinol) resulted in polycyclic structures containing a nitrosulfolane ring fused with chromane system,[11] while the reactions with N,N-binucleophiles – phenylhydrazine and semicarbazide – served as a foundation for the development of effective methods for the synthesis of bicyclic nitrosulfolane derivatives containing a pyrazolidine ring.[12,13] It should be noted that our proposed procedures for the formation of pyrazolidine structures were performed under mild conditions[12,13] (room temperature, without catalysts), in contrast to the traditional synthesis of pyrazolidines through dipolar cycloaddition reactions.[14]

For the purpose of extending this method to the construction of structurally related sulfolane-containing bicyclic systems, we studied the reactions of 2-benzylidene-3-methyl-4-nitro-3-thiolene 1,1-dioxides **1a**–**f** with N,O-binucleophiles – hydroxylamine (**2a**) and *N*-methylhydroxylamine (**2b**) (Scheme 1). The synthesis of target compounds containing a fused isoxazolidine system is of interest due to the fact that the isoxazole ring and its hydrogenated derivatives are present as structural motifs in a range of natural compounds,[15] β-lactam antibiotics,[16] as well as in biologically active compounds with antibacterial[17] and cytotoxic[18] properties.

The previously used conditions[12,13] for the synthesis of pyrazolidine-containing bicyclic nitrosulfolane derivatives (ethanol, 18°C, 24 h) were found to be ineffective for the reaction between nitrosulfodienes **1a**–**f** and hydroxylamine

†Deceased.

Scheme 1



(**2a**), since the bicyclic target compounds **3a**–**f** formed in these reactions were isolated as 1:6 mixtures of two diastereomers. Performing the reaction in DMSO led to a different ratio of stereoisomers **3a**–**f** (10:1 according to the data of ^{1}H NMR spectroscopy), allowing to isolate the major diastereomers as individual compounds in 43–75% yields. The highly electron-deficient nature of nitro-substituted diene **1e** was the reason why it was the most reactive toward hydroxylamine (**2a**), giving the maximum yield of bicyclic product **3e**. In the case of bicyclic derivatives **3c**,**f** that were obtained on the basis of benzylidenenitrothiolene 1,1-dioxides **1c**,**f** containing electron-donating substituents (4-MeC_6H_4, furan-2-yl), the yields did not exceed 55% (Scheme 1, Table 1).

The reaction of dienes **1a**–**f** with *N*-methylhydroxylamine (**2b**) proceeded in ethanol (18°C, 72 h) with the formation of bicyclic compounds **4a**–**f**, which were isolated in the form of individual diastereomers in 25–56% yields (Scheme 1, Table 1).

It can be logically assumed that the formation of products **3**, **4 a**–**f**, similarly to the case of pyrazolidine-containing analogs,[12,13] resulted from a tandem process that included the initial nucleophilic addition step of the reagent at positions 1 and 4 of dienes and subsequent heterocyclization *via* secondary addition step involving the OH group. The proposed role of Δ^3-isomeric form in the latter transformation was supported by the preference for 5-*exo*-*trig*-cyclization[19] and the pronounced lability of the multiple bond in nitrothiolene dioxides in the presence of polar solvents.[10]

Compounds **3**, **4 a**–**f** were isolated as colorless crystals that were stable during storage at room temperature. Their structures were confirmed by IR spectroscopy, one-dimensional ^{1}H and ^{13}C NMR spectroscopy, as well as ^{1}H–^{13}C HMQC and ^{1}H–^{13}C HMBC experiments. It should be noted that the spectral characteristics of the synthesized isoxazolidine-containing nitrosulfolane derivatives **3**, **4 a**–**f** were in agreement with the properties of the previously obtained pyrazolidine-containing analogs.[12,13]

IR spectra of the bicyclic products **3**, **4 a**–**f** showed absorption bands due to an unconjugated nitro group (1350−1373, 1548−1569 cm^{-1}) and sulfonyl group (1122−1145, 1309−1339 cm^{-1}), while the spectra of products **3a**–**f** additionally contained absorption bands due to NH bond vibrations (3219−3303 cm^{-1}).

Table 1. Yields of products **3**, **4 a**–**f**

Diene	Ar	Product (yield, %)	Product (yield, %)
1a	Ph	**3a** (70)	**4a** (52)
1b	4-BrC_6H_4	**3b** (70)	**4b** (40)
1c	4-MeC_6H_4	**3c** (55)	**4c** (41)
1d	4-ClC_6H_4	**3d** (73)	**4d** (30)
1e	4-$NO_2C_6H_4$	**3e** (75)	**4e** (56)
1f	Furan-2-yl	**3f** (43)	**4f** (25)

Compounds **3**, **4 a**–**f** had generally similar ^{1}H NMR spectra that contained all of the expected proton signals of the structural parts in these molecules. For example, the methyl group protons in ^{1}H NMR spectrum of bicyclic compound **3b** appeared as a singlet at 1.35 ppm; the 5-CH_2 methylene protons and the nitromethine proton (6-CH) formed a strongly coupled three-spin ABX system observed as three double doublets at 3.94, 4.13, and 5.40 ppm ($^2J_{AB}$ = 13.7, $^3J_{AX}$ = 6.6, $^3J_{BX}$ = 11.5 Hz). The proton at the C-3 atom gave a double doublet at 5.09 ppm, forming an AMX system ($^3J_{AM}$ = 2.1, $^3J_{MX}$ = 5.5 Hz) with the methine proton at the C-3a atom (4.14 ppm) and the proton bonded to the nitrogen atom (7.01 ppm). The downfield region (7.33, 7.52 ppm) contained two doublets that were assigned to the protons of benzene ring. Identical ^{1}H NMR characteristics were also observed in the case of bicyclic products **3a**,**d**,**e**.

^{1}H NMR spectra of compounds **3c**,**f**, **4a**–**f** had several distinguishing features pointing to a different spatial arrangement compared to bicyclic products **3a**,**b**,**d**,**e**. The spectra of compounds **3c**,**f** showed a characteristic downfield shift of methyl group protons to 1.80−1.82 ppm, as well as the presence of a remote coupling between the 5-CH_A methylene group proton and the 3a-CH methine group proton (^4J = 1.8 Hz). In the case of bicyclic products **4a**–**f**, the downfield appearance of methyl group protons (1.81−1.86 ppm) was accompanied by an upfield shift of the 3-CH proton signal to 4.09−4.18 ppm.

According to the results of X-ray structural analysis, all chiral centers in the molecule of product **3b** had (*R*)-configuration. The close similarity of ^{1}H NMR spectra of compounds **3a**,**b**,**d**,**e** allow to logically propose that compounds **3a**,**d**,**e** were also isolated as 3*R**,3a*R**,6*R**,6a*R**-

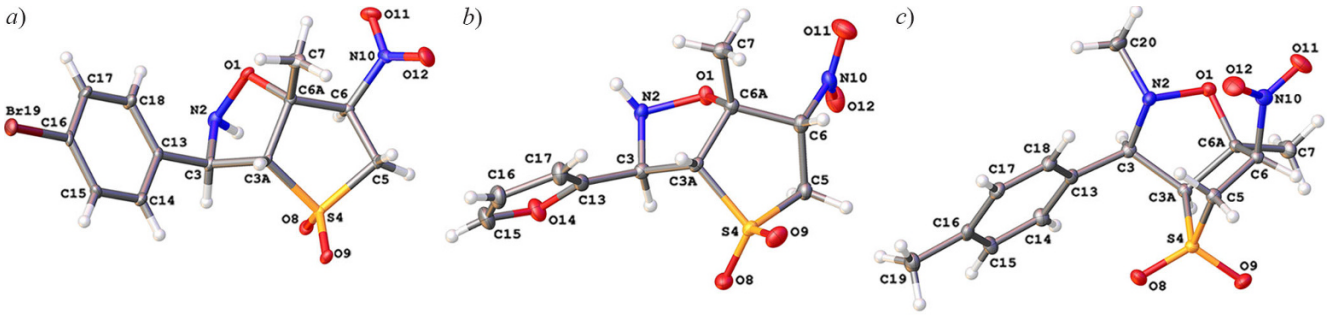


Figure 1. The molecular structures of compounds *a*) **3b**, *b*) **3f**, and *c*) **4c** with atoms represented by thermal vibration ellipsoids of 50% probability.

isomers. Analogously, by taking into account the data of X-ray structural analysis and ^{1}H NMR spectroscopy, 3*R**,3a*R**,6*S**,6a*R** configuration was assigned to products **3c**,**f** and 3*R**,3a*S**,6*R**,6a*S** configuration to bicyclic compounds **4a**–**f**.

According to the data of X-ray structural analysis, the unit cells in the crystal structure of all three compounds **3b**,**f**, **4c** contained a single bicyclic molecule (Fig. 1*a*–*c*). All of the molecules had similar bond lengths, valence and torsion angles, but certain spatial structure features could be distinguished in each case. The most distinct structure was that of compound **4c**, with (*S*,*S*)-configuration of the C-3a,6a atoms.

The molecular packing of all bicyclic products (Fig. 2*a*,*b*, 3*a*–*c*) was realized by a network of intermolecular hydrogen bonds involving the hydrogen atoms of methyl and methylene groups, as well as the oxygen atoms of sulfonyl and nitro groups. It should be noted that an additional π–π interaction of furan rings occurred between the molecules of compound **3f** (Fig. 3*c*).

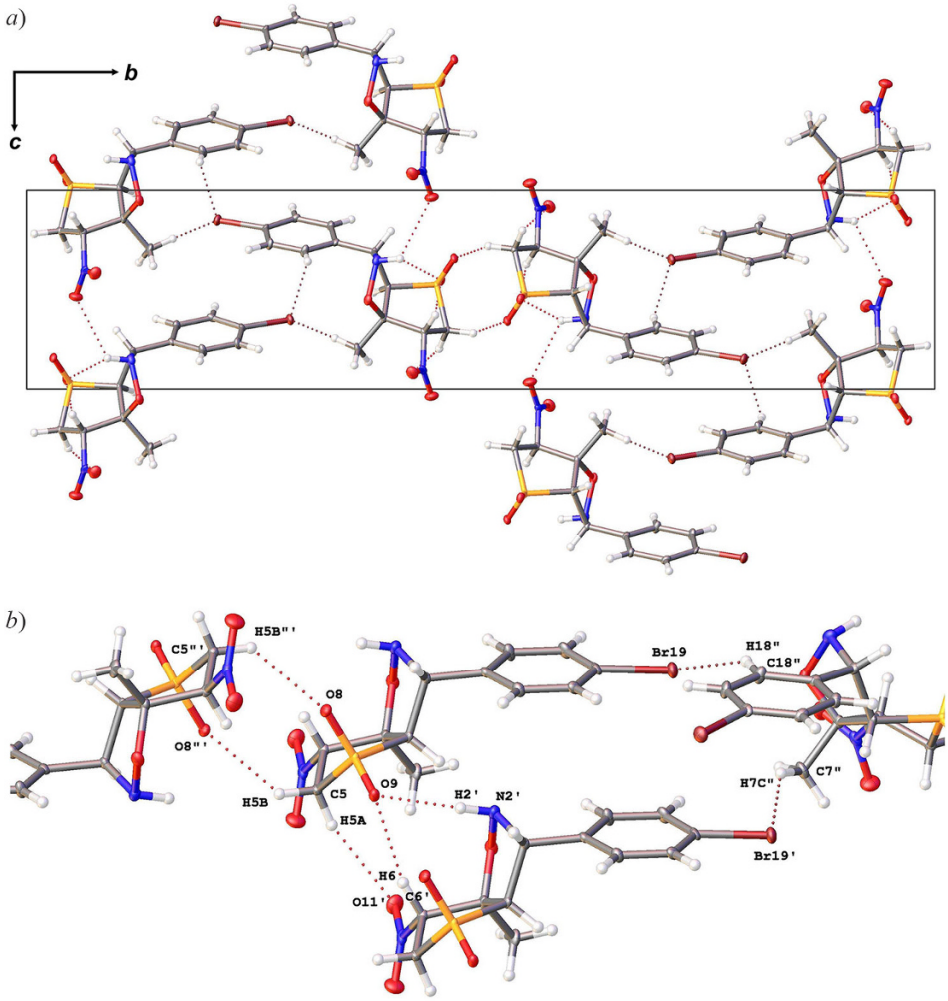


Figure 2. *a*) The molecular packing in crystal of compound **3b**, *b*) hydrogen bonding pattern in the structure of compound **3b**.

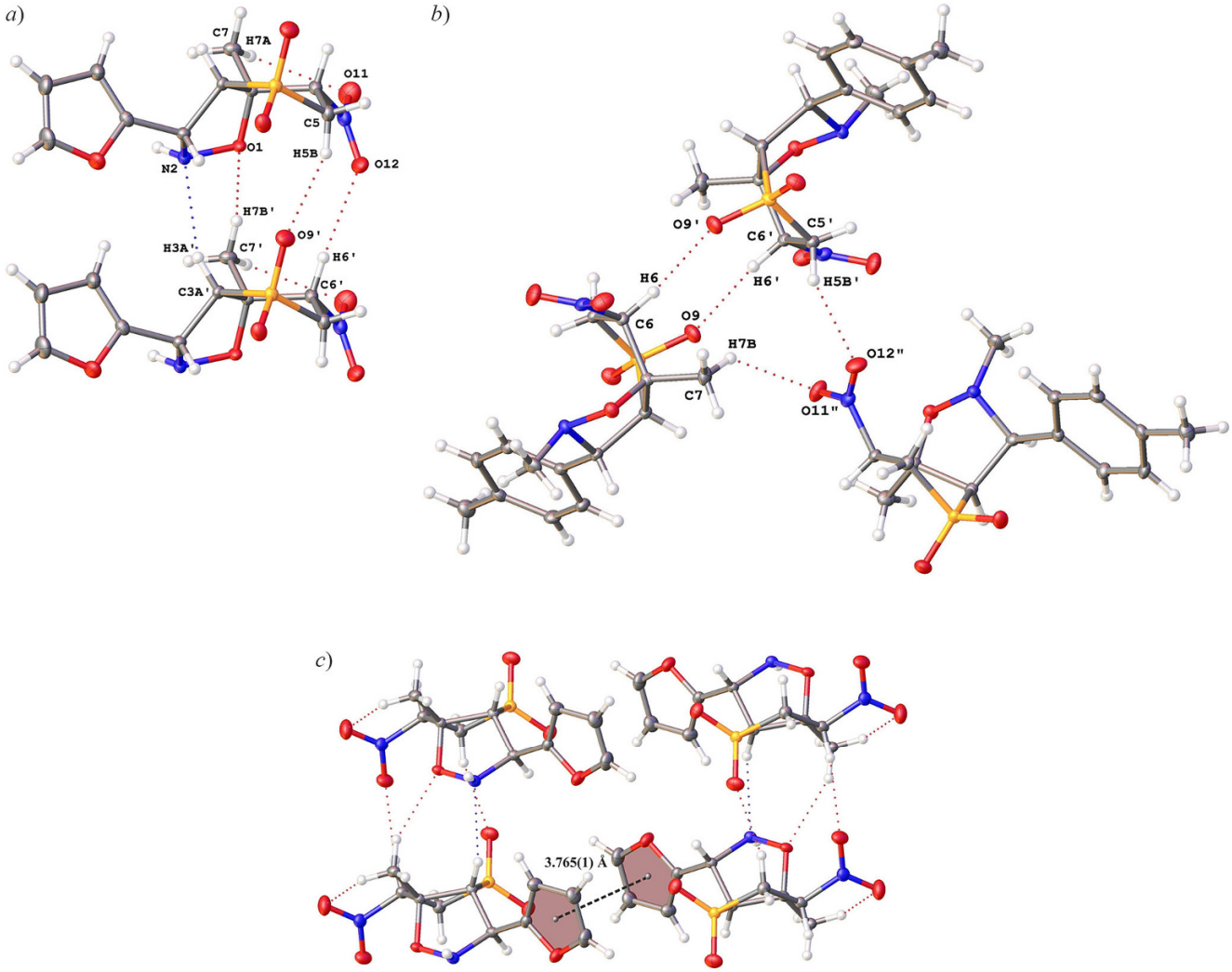


Figure 3. The hydrogen bonding network in the structures of compounds *a*) **3f** and *b*) **4c**; *c*) π–π interaction between the furan rings in the structure of compound **3f**.

Thus, we have demonstrated that the reactions of nitrosulfodienes of thiolene 1,1-dioxide series with hydroxylamine and *N*-methylhydroxylamine at room temperature provided good yields of bicyclic structures combining fused isoxazolidine and nitrosulfolane rings.

Experimental

IR spectra were recorded on a Shimadzu IRPrestige-21 FTIR spectrometer in KBr pellets. ^{1}H, ^{13}C, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC NMR spectra were acquired on a Jeol ECX400A spectrometer at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei in CD_3CN solution. Residual non-deuterated solvent signals (1.92 ppm for ^{1}H NMR spectra) and deuterated solvent signals (0.42 ppm for ^{13}C NMR spectra) were used as internal standards. Elemental analysis was performed on a Eurovector EuroEA3000 analyzer (CHN Dual mode). Melting points were determined on a PTP(M) apparatus (specification TU 92-891.001-90).

The starting nitrosulfodienes **1a–f** were obtained according to published procedures.[10,20]

(3*R,3a*R**,6*R**,6a*R**)-6a-Methyl-6-nitro-3-phenylhexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (3a)**. Aqueous 1 M NaOH solution (2 ml) was added to hydroxylamine hydrochloride (**2a**) (140 mg, 2 mmol). The obtained solution was poured into a stirred solution of nitrosulfodiene **1a** (265 mg, 1 mmol) in DMSO (10 ml). The reaction mixture was stirred for 24 h at room temperature, then poured onto crushed ice (20 ml). The obtained precipitate contained a mixture of diastereomers (3*R**,3a*R**,6a*R**,6*R**) in 9:1 ratio according to the data of ^{1}H NMR spectra. The product was collected on a Schott filter, washed with distilled water, ethanol, and air-dried. Yield 208 mg (70%), white powder, mp 160–162°C (EtOH). IR spectrum, ν, cm^{-1}: 1134, 1309 (SO_2), 1369, 1555 (NO_2), 3279, 3296 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): major diastereomer: 1.37 (3H, s, CH_3); 3.95 (1H, dd, ^{2}J = 13.7, ^{3}J = 6.7, 5-CH_2); 4.04 (1H, dd, ^{2}J = 13.7, ^{3}J = 11.6, 5-CH_2); 4.14 (1H, d,

^3J = 2.1, 3a-CH); 5.09 (1H, dd, ^3J = 5.9, ^3J = 2.1, 3-CH); 5.40 (1H, dd, ^3J = 11.6, ^3J = 6.7, 6-CH); 6.97 (1H, d, ^3J = 5.9, NH); 7.28–7.43 (5H, m, H Ph); minor diastereomer: 1.52 (3H, s, CH_3); 3.67–3.69 (1H, m, 5-CH_2); 3.90–3.92 (1H, m, 5-CH_2); 4.54 (1H, br. s, 3a-CH); 5.00–5.02 (1H, m, 3-CH); 5.41–5.43 (1H, m, 6-CH); 6.98 (1H, br. s, NH); 7.28–7.43 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 19.6 (CH_3); 53.4 (C-5); 65.9 (C-3); 75.2 (C-3a); 86.6 (C-6); 93.3 (C-6a); 126.9 (C Ph); 127.8 (2C Ph); 128.6 (2C Ph); 133.4 (C Ph). Found, %: C 48.17; H 4.88; N 9.23. $C_{12}H_{14}N_2O_5S$. Calculated, %: C 48.32; H 4.73; N 9.39.

(3*R,3a*R**,6*R*,*6a*R**)-3-(4-Bromophenyl)-6a-methyl-6-nitrohexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (3b)** was obtained analogously to compound **3a** from nitrosulfodiene **1b** (344 mg, 1 mmol) and hydroxylamine hydrochloride (**2a**) (140 mg, 2 mmol). Yield 274 mg (70%), white powder, mp 183–185°C (EtOH). IR spectrum, ν, cm^{-1}: 1123, 1318 (SO_2), 1368, 1551 (NO_2), 3272, 3302 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (3H, s, CH_3); 3.94 (1H, dd, ^2J = 13.7, ^3J = 6.6, 5-CH_2); 4.13 (1H, dd, ^2J = 13.7, ^3J = 11.5, 5-CH_2); 4.14 (1H, d, ^3J = 2.1, 3a-CH); 5.09 (1H, dd, ^3J = 5.5, ^3J = 2.1, 3-CH); 5.40 (1H, dd, ^3J = 11.5, ^3J = 6.6, 6-CH); 7.01 (1H, d, ^3J = 5.5, NH); 7.33 (2H, d, ^3J = 8.2, H Ar); 7.52 (2H, d, ^3J = 8.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 19.4 (CH_3); 53.5 (C-5); 65.8 (C-3); 75.2 (C-3a); 86.4 (C-6); 93.6 (C-6a); 122.2 (C Ar); 130.2 (2C Ar); 131.3 (2C Ar); 132.3 (C Ar). Found, %: C 38.51; H 3.13; N 7.65. $C_{12}H_{13}BrN_2O_5S$. Calculated, %: C 38.21; H 3.47; N 7.43.

(3*R,3a*R**,6*S**,6a*R**)-6a-Methyl-3-(4-methylphenyl)-6-nitrohexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (3c)** was obtained analogously to compound **3a** from nitrosulfodiene **1c** (279 mg, 1 mmol) and hydroxylamine hydrochloride (**2a**) (140 mg, 2 mmol). Yield 172 mg (55%), white powder, mp 185–189°C (EtOH). IR spectrum, ν, cm^{-1}: 1122, 1318 (SO_2), 1364, 1556 (NO_2), 3219, 3243 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (3H, s, CH_3); 2.31 (3H, s, CH_3 Ar); 3.77 (1H, ddd, ^2J = 13.7, ^3J = 6.7, ^4J = 1.8, 5-CH_2); 3.93 (1H, dd, ^3J = 6.4, ^4J = 1.8, 3a-CH); 4.19 (1H, dd, ^2J = 13.7, ^3J = 12.2, 5-CH_2); 4.92 (1H, dd, ^3J = 10.7, ^3J = 6.4, 3-CH); 5.28 (1H, dd, ^3J = 12.2, ^3J = 6.7, 6-CH); 6.51 (1H, d, ^3J = 10.7, NH); 7.20 (2H, d, ^3J = 8.2, H Ar); 7.31 (2H, d, ^3J = 8.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.5 (CH_3); 20.2 (CH_3 Ar); 49.6 (C-5); 68.6 (C-3); 80.1 (C-3a); 83.8 (C-6); 90.5 (C-6a); 126.7 (C Ar); 127.7 (2C Ar); 129.6 (2C Ar); 138.8 (C Ar). Found, %: C 50.29; H 5.33; N 8.83. $C_{13}H_{16}N_2O_5S$. Calculated, %: C 49.99; H 5.16; N 8.97.

(3*R,3a*R**,6*R**,6a*R**)-3-(4-Chlorophenyl)-6a-methyl-6-nitrohexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (3d)** was obtained analogously to compound **3a** from nitrosulfodiene **1d** (300 mg, 1 mmol) and hydroxylamine hydrochloride (**2a**) (140 mg, 2 mmol). Yield 242 mg (73%), white powder, mp 165–167°C (EtOH). IR spectrum, ν, cm^{-1}: 1125, 1319 (SO_2), 1364, 1548 (NO_2), 3272, 3303 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): major diastereomer: 1.35 (3H, s, CH_3); 3.95 (1H, dd, ^2J = 13.8, ^3J = 6.7, 5-CH_2); 4.04 (1H, dd, ^2J = 13.8, ^3J = 11.6, 5-CH_2); 4.13 (1H, d, ^3J = 1.8, 3a-CH); 5.10 (1H, dd, ^3J = 5.3, ^3J = 1.8, 3-CH); 5.40 (1H, dd, ^3J = 11.6, ^3J = 6.7, 6-CH); 7.02 (1H, d, ^3J = 5.3, NH); 7.30 (2H, d, ^3J = 7.9, H Ar); 7.36 (2H, d, ^3J = 7.9, H Ar); minor diastereomer: 1.52 (3H, s, CH_3); 3.68–3.70 (1H, m, 5-CH_2); 3.89–3.91 (1H, m, 5-CH_2); 4.52 (1H, br. s, 3a-CH); 4.95–4.97 (1H, m, 3-CH); 5.40–5.43 (1H, m, 6-CH); 6.98 (1H, br. s, NH); 7.30 (2H, d, ^3J = 7.9, H Ar), 7.36 (2H, d, ^3J = 7.9, H Ar). ^{13}C NMR spectrum, δ, ppm: 19.6 (CH_3); 53.5 (C-5); 65.9 (C-3); 75.1 (C-3a); 86.6 (C-6); 93.4 (C-6a); 125.5 (C Ar); 131.2 (2C Ar); 133.4 (2C Ar); 137.5 (C Ar). Found, %: C 43.79; H 4.04; N 8.26. $C_{12}H_{13}ClN_2O_5S$. Calculated, %: C 43.31; H 3.94; N 8.42.

(3*R,3a*R**,6*R**,6a*R**)-6a-Methyl-6-nitro-3-(4-nitrophenyl)hexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (3e)** was obtained analogously to compound **3a** from nitrosulfodiene **1e** (310 mg, 1 mmol) and hydroxylamine hydrochloride (**2a**) (69.5 mg, 1 mmol). Yield 257 mg (75%), white powder, mp 180–184°C (EtOH). IR spectrum, ν, cm^{-1}: 1129, 1314 (SO_2), 1350, 1558 (NO_2), 3276, 3315 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, s, CH_3); 3.99 (1H, dd, ^2J = 13.8, ^3J = 6.7, 5-CH_2); 4.20 (1H, dd, ^2J = 13.8, ^3J = 12.5, 5-CH_2); 4.30 (1H, d, ^3J = 6.7, 3a-CH); 5.14 (1H, dd, ^3J = 8.2, ^3J = 6.7, 3-CH); 5.31 (1H, dd, ^3J = 12.5, ^3J = 6.7, 6-CH); 7.13 (1H, d, ^3J = 8.2, NH), 7.53–7.56 (2H, m, H Ar); 8.14–8.22 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 19.8 (CH_3); 53.7 (C-5); 66.1 (C-3); 76.3 (C-3a); 86.6 (C-6); 93.4 (C-6a); 127.4 (C Ar); 131.3 (2C Ar); 132.9 (2C Ar); 133.5 (C Ar). Found, %: C 41.65; H 3.73; N 12.56. $C_{12}H_{13}N_3O_7S$. Calculated, %: C 41.98; H 3.82; N 12.24.

(3*R,3a*R**,6*S**,6a*R**)-3-(Furan-2-yl)-6a-methyl-6-nitrohexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (3f)** was obtained analogously to compound **3a** from nitrosulfodiene **1f** (255 mg, 1 mmol) and hydroxylamine hydrochloride (**2a**) (350 mg, 5 mmol). Yield 124 mg (43%), white powder, mp 162–164°C (EtOH). IR spectrum, ν, cm^{-1}: 1130, 1318 (SO_2), 1371, 1555 (NO_2), 3225 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.82 (3H, s, CH_3); 3.79 (1H, ddd, ^2J = 13.7, ^3J = 6.7, ^4J = 1.8, 5-CH_2); 4.05 (1H, dd, ^3J = 5.2, ^4J = 1.8, 3a-CH); 4.15 (1H, dd, ^2J = 13.7, ^3J = 12.2, 5-CH_2); 5.05 (1H, dd, ^3J = 9.3, ^3J = 5.2, 3-CH); 5.31 (1H, dd, ^3J = 12.2, ^3J = 6.7, 6-CH); 6.42 (1H, dd, ^3J = 3.4, ^3J = 1.8, H furan); 6.50 (1H, d, ^3J = 3.4, H furan); 6.55 (1H, d, ^3J = 9.3, NH); 7.52 (1H, d, ^3J = 1.8, H furan). ^{13}C NMR spectrum, δ, ppm: 22.5 (CH_3); 50.1 (C-5); 68.1 (C-3); 80.2 (C-3a); 84.1 (C-6); 90.4 (C-6a); 110.2 (C furan); 110.6 (C furan); 143.5 (C furan); 145.1 (C furan). Found, %: C 41.31; H 3.80; N 9.49. $C_{10}H_{12}N_2O_6S$. Calculated, %: C 41.67; H 4.20; N 9.72.

(3*R,3a*S**,6*R**,6a*S**)-2,6a-Dimethyl-6-nitro-3-phenylhexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (4a)**. Aqueous 1 M NaOH solution (1 ml) was added to *N*-methylhydroxylamine hydrochloride (**2b**) (84 mg, 1 mmol). The obtained solution was poured into a suspension of nitrosulfodiene **1a** (265 mg, 1 mmol) in ethanol (10 ml). The reaction mixture was stirred for 72 h at room temperature, the obtained precipitate was collected on a Schott filter, washed with ethanol, and air-dried. Yield 162 mg (52%), white powder, mp 157–160°C (EtOH). IR spectrum, ν, cm^{-1}:

1134, 1332 (SO_2), 1373, 1569 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (3H, s, CH_3); 2.54 (3H, s, NCH_3); 3.66 (1H, ddd, ^2J = 12.9, ^3J = 6.7, ^4J = 2.1, 5-CH_2); 3.99 (1H, dd, ^3J = 7.2, ^4J = 2.1, 3a-CH); 4.15 (1H, d, ^3J = 7.2, 3-CH); 4.18 (1H, dd, ^2J = 12.9, ^3J = 12.2, 5-CH_2); 5.18 (1H, dd, ^3J = 12.2, ^3J = 6.7, 6-CH); 7.29–7.34 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 24.5 (CH_3); 42.5 (NCH_3); 52.8 (C-5); 73.9 (C-3); 76.3 (C-3a); 83.9 (C-6); 85.8 (C-6a); 128.2 (3C Ph); 128.6 (2C Ph); 131.9 (C Ph). Found, %: C 49.89; H 5.26; N 8.67. $C_{13}H_{16}N_2O_5S$. Calculated, %: C 49.99; H 5.16; N 8.97.

(3*R,3a*S**,6*R**,6a*S**)-3-(4-Bromophenyl)-2,6a-dimethyl-6-nitrohexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (4b)** was obtained analogously to compound **4a** from nitrosulfodiene **1b** (344 mg, 1 mmol) and *N*-methylhydroxylamine hydrochloride (**2b**) (84 mg, 1 mmol). Yield 156 mg (40%), white powder, mp 165–170°C (EtOH). IR spectrum, ν, cm^{-1}: 1145, 1339 (SO_2), 1368, 1557 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (3H, s, CH_3); 2.53 (3H, s, NCH_3); 3.69 (1H, ddd, ^2J = 13.0, ^3J = 6.8, ^4J = 2.2, 5-CH_2); 3.99 (1H, dd, ^3J = 7.2, ^4J = 2.2, 3a-CH); 4.12 (1H, d, ^3J = 7.2, 3-CH); 4.14 (1H, dd, ^2J = 13.0, ^3J = 12.2, 5-CH_2); 5.18 (1H, dd, ^3J = 12.2, ^3J = 6.8, 6-CH); 7.27 (2H, d, ^3J = 8.4, H Ar); 7.51 (2H, d, ^3J = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 24.5 (CH_3); 42.4 (NCH_3); 52.9 (C-5); 73.2 (C-3); 76.0 (C-3a); 84.0 (C-6); 85.7 (C-6a); 121.6 (C Ar); 130.6 (2C Ar); 131.2 (2C Ar); 131.5 (C Ar). Found, %: C 39.43; H 3.96; N 7.02. $C_{13}H_{15}BrN_2O_5S$. Calculated, %: C 39.91; H 3.86; N 7.16.

(3*R,3a*S**,6*R**,6a*S**)-2,6a-Dimethyl-3-(4-methylphenyl)-6-nitrohexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (4c)**. Aqueous 1 M NaOH solution (2 ml) was added to *N*-methylhydroxylamine hydrochloride (**2b**) (167 mg, 2 mmol). The obtained solution was poured into a suspension of nitrosulfodiene **1c** (279 mg, 1 mmol) in ethanol (10 ml). The reaction mixture was maintained for 72 h at room temperature, the obtained precipitate was collected on a Schott filter, washed with ethanol, and air-dried. Yield 133 mg (41%), white powder, mp 153–157°C (EtOH). IR spectrum, ν, cm^{-1}: 1132, 1324 (SO_2), 1370, 1556 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (3H, s, CH_3); 2.31 (3H, s, CH_3 Ar); 2.53 (3H, s, NCH_3); 3.65 (1H, ddd, ^2J = 12.8, ^3J = 6.7, ^4J = 2.1, 5-CH_2); 3.94 (1H, dd, ^3J = 7.2, ^4J = 2.1, 3a-CH); 4.09 (1H, d, ^3J = 7.2, 3-CH); 4.17 (1H, dd, ^2J = 12.8, ^3J = 12.2, 5-CH_2); 5.18 (1H, dd, ^3J = 12.2, ^3J = 6.7, 6-CH); 7.16 (2H, d, ^3J = 7.9, H Ar); 7.21 (2H, d, ^3J = 7.9, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.3 (CH_3 Ar); 24.5 (CH_3); 42.5 (NCH_3); 52.8 (C-5); 73.9 (C-3); 76.2 (C-3a); 83.9 (C-6); 85.8 (C-6a); 128.5 (C Ar); 128.8 (2C Ar); 128.9 (2C Ar); 138.1 (C Ar). Found, %: C 51.20; H 5.90; N 8.32. $C_{14}H_{18}N_2O_5S$. Calculated, %: C 51.52; H 5.56; N 8.58.

(3*R,3a*S**,6*R**,6a*S**)-3-(4-Chlorophenyl)-2,6a-dimethyl-6-nitrohexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (4d)** was obtained analogously to compound **4a** from nitrosulfodiene **1d** (300 mg, 1 mmol) and *N*-methylhydroxylamine hydrochloride (**2b**) (84 mg, 1 mmol). Yield 104 mg (30%), white powder, mp 164–166°C (EtOH). IR spectrum, ν, cm^{-1}: 1144, 1339 (SO_2), 1367, 1563 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (3H, s, CH_3); 2.54 (3H, s, NCH_3); 3.69 (1H, ddd, ^2J = 13.1, ^3J = 6.7, ^4J = 2.1, 5-CH_2); 4.00 (1H, dd, ^3J = 7.1, ^4J = 2.1, 3a-CH); 4.14 (1H, d, ^3J = 7.1, 3-CH); 4.16 (1H, dd, ^2J = 13.1, ^3J = 12.2, 5-CH_2); 5.20 (1H, dd, ^3J = 12.2, ^3J = 6.7, 6-CH); 7.32 (2H, d, ^3J = 8.8, H Ar); 7.36 (2H, d, ^3J = 8.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 24.4 (CH_3); 42.5 (NCH_3); 52.8 (C-5); 73.2 (C-3); 76.2 (C-3a); 84.1 (C-6); 85.7 (C-6a); 128.3 (C Ar); 130.7 (2C Ar); 133.3 (2C Ar); 137.1 (C Ar). Found, %: C 44.57; H 3.98; N 7.59. $C_{13}H_{15}ClN_2O_5S$. Calculated, %: C 45.03; H 4.36; N 8.08.

(3*R,3a*S**,6*R**,6a*S**)-2,6a-Dimethyl-6-nitro-3-(4-nitrophenyl)hexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (4e)** was obtained analogously to compound **4a** from nitrosulfodiene **1e** (310 mg, 1 mmol) and *N*-methylhydroxylamine (**2b**) (84 mg, 1 mmol). Yield 200 mg (56%), white powder, mp 145–148°C (EtOH). IR spectrum, ν, cm^{-1}: 1134, 1336 (SO_2), 1367, 1563 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.86 (3H, s, CH_3); 2.58 (3H, s, NCH_3); 3.70 (1H, ddd, ^2J = 13.1, ^3J = 6.7, ^4J = 2.1, 5-CH_2); 4.11 (1H, dd, ^3J = 7.3, ^4J = 2.1, 3a-CH); 4.14 (1H, d, ^3J = 7.3, 3-CH); 4.17 (1H, dd, ^2J = 13.1, ^3J = 12.2, 5-CH_2); 5.21 (1H, dd, ^3J = 12.2, ^3J = 6.7, 6-CH); 7.60 (2H, d, ^3J = 8.8, H Ar); 8.17 (2H, d, ^3J = 8.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 24.4 (CH_3); 42.3 (NCH_3); 52.9 (C-5); 74.0 (C-3); 76.3 (C-3a); 83.9 (C-6); 85.8 (C-6a); 127.3 (2C Ar); 130.3 (C Ar); 133.0 (2C Ar); 133.7 (C Ar). Found, %: C 44.17; H 4.72; N 12.05. $C_{13}H_{15}N_3O_7S$. Calculated, %: C 43.70; H 4.23; N 11.76.

(3*R,3a*S**,6*R**,6a*S**)-3-(Furan-2-yl)-2,6a-dimethyl-6-nitrohexahydrothieno[2,3-*d*]isoxazole 4,4-dioxide (4f)**. Aqueous 1 M NaOH solution (5 ml) was added to *N*-methylhydroxylamine hydrochloride (**2b**) (417 mg, 5 mmol). The obtained solution was poured into a suspension of nitrosulfodiene **1f** (255 mg, 1 mmol) in ethanol (10 ml). The reaction mixture was maintained for 72 h at room temperature, the obtained precipitate was collected on a Schott filter, washed with ethanol, and air-dried. Yield 76 mg (25%), white powder, mp 149–153°C (EtOH). IR spectrum, ν, cm^{-1}: 1133, 1317 (SO_2), 1372, 1559 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81 (3H, s, CH_3); 2.54 (3H, s, NCH_3); 3.67 (1H, ddd, ^2J = 13.1, ^3J = 6.7, ^4J = 2.4, 5-CH_2); 3.92 (1H, dd, ^3J = 7.9, ^4J = 2.4, 3a-CH); 4.18 (1H, d, ^3J = 7.9, 3-CH); 4.21 (1H, dd, ^2J = 13.1, ^3J = 12.0, 5-CH_2); 5.17 (1H, dd, ^3J = 12.0, ^3J = 6.7, 6-CH); 6.37 (1H, d, ^3J = 3.2, H furan); 6.40 (1H, dd, ^3J = 3.2, ^3J = 2.1, H furan); 7.51 (1H, d, ^3J = 2.1, H furan). ^{13}C NMR spectrum, δ, ppm: 24.3 (CH_3); 42.6 (NCH_3); 52.6 (C-5); 68.3 (C-3); 74.2 (C-3a); 84.4 (C-6); 86.0 (C-6a); 110.2 (C furan); 110.7 (C furan); 143.3 (C furan); 145.0 (C furan). Found, %: C 43.26; H 4.87; N 9.72. $C_{11}H_{14}N_2O_6S$. Calculated, %: C 43.71; H 4.67; N 9.27.

X-ray structural analysis of compounds 3b,f, 4c was performed at 100 K on Rigaku Oxford Diffraction Xcalibur Eos (monochromatic microfocus MoKα radiation, compound **3b**), Rigaku Oxford Diffraction SuperNova Atlas (monochromatic microfocus CuKα radiation, compound **3f**), and Bruker Kappa Apex II DUO (monochromatic microfocus MoKα radiation, compound **4c**) diffractometers that were equipped with planar CCD detectors.

The obtained data were integrated with corrections for Lorentz background and polarization effects using the CrysAlisPro software suite[21] (for compounds **3f**,**b**) or Bruker APEX2 and XPREP software (for compounds **4c**). The correction for absorption in the case of compounds **3f**,**b** was introduced empirically with CrysAlisPro software suite, using spherical harmonics implemented with the SCALE3 ABSPACK scaling algorithm or the SADABS program for compound **4c**.[22] The structures were solved by direct methods and refined by using the SHELX program[23] within the OLEX2 software suite.[24] The hydrogen atom positions were calculated by algorithms incorporated in the SHELX software suite where U_{iso}(H) was set as 1.5U_{eq}(C) and C–H bond length was 0.96 Å for CH_3 groups, U_{iso}(H) was set as 1.2U_{eq}(C) and C–H bond length was 0.97 Å for CH_2 groups, U_{iso}(H) was set as 1.2U_{eq}(C) and C–H bond length was 0.93 Å for CH groups in cyclic moieties, U_{iso}(H) was set as 1.2U_{eq}(C) and C–H bond length was 0.98 Å for tertiary CH groups, and U_{iso}(H) was set as 1.2U_{eq}(N) and N–H bond length was 0.86 Å for NH groups.

Compounds **3b**,**f** and **4c** crystallized in monoclinic syngony, space group $P2_1/c$. Compound **3b**: *a* 5.8141(3), *b* 32.9213(14), *c* 7.3228(4) Å; β 100.376(5)°; *V* 1378.72(12) Å^3; *Z* 4, 2θ 5.79–60.00°, R_1 0.040, wR_2 0.078 (for 3431 reflections with $|F_o| \geq 4\sigma_F$); *S* 1.099. Compound **3f**: *a* 17.7558(11), *b* 5.2441(3), *c* 13.6905(9) Å; β 109.448(7)°; *V* 1202.04(14) Å^3; *Z* 4, 2θ 10.57–145.00°, R_1 0.038, wR_2 0.102 (for 2178 reflections with $|F_o| \geq 4\sigma_F$); *S* 1.048. Compound **4c**: *a* 14.9756(15), *b* 11.7644(13), *c* 8.5652(9) Å; β 95.443(2)°; *V* 1502.2(3) Å^3; *Z* 4; 2θ 4.41–60.00°, R_1 0.033, wR_2 0.086 (for 3458 reflections with $|F_o| \geq 4\sigma_F$); *S* 1.056.

The complete crystallographic datasets for compounds **3b**,**f** and **4c** were deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1576187, CCDC 1559533, CCDC 1559534, respectively).

A Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all synthesized compounds, as well as ^{1}H–^{13}C HMQC and ^{1}H–^{13}C HMBC spectra of compounds **3c**, **4a**–**c** is available at the journal website at http://link.springer.com/journal/10593.

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The X-ray crystallography studies were performed on the equipment of the Saint Petersburg State University resource center "X-ray diffraction methods".

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