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New approaches to the synthesis of 2,5-dihydro-1,5-benzothiazepines containing nitro groups

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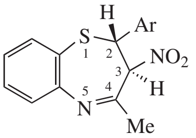
Reaction between *o*-aminothiophenol and 4-(2-furyl)-3-nitrobut-3-en-2-one affords 4-methyl-3-nitro-2-(2-furyl)-2,5-dihydro-1,5-benzothiazepine whose structure was characterized by X-ray diffraction analysis.

Pharmaceuticals whose molecules contain the 1,5-benzothiazepine moiety are widely used in medical practice. For example, Diltiazem manifests antianginal, antihypertensive and antiarrhythmic properties, and Quetiapine belongs to neuroleptics.[1–4]

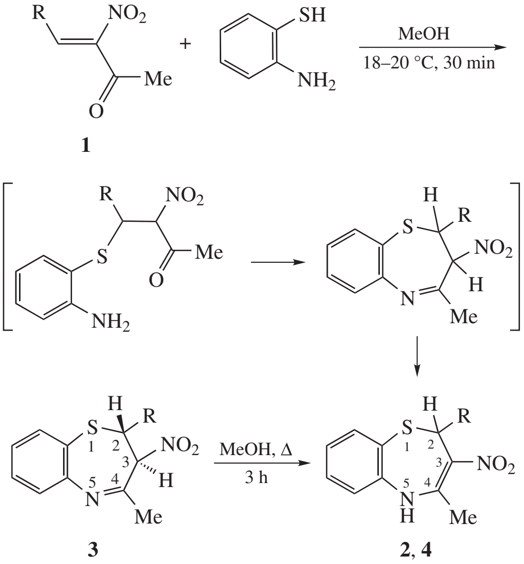
Previously, we reported a one-pot synthesis of 2-aryl-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepines **A** by condensation of *gem*-acetylnitrostyrenes with *o*-aminothiophenol.[5,6]



A

Ar = Ph, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$

To expand the scope of similar dihydrobenzothiazepines, it is of interest to move to *gem*-acetylnitroethenes containing pharmacophoric heterocycles. In this work we studied the condensation of *o*-aminothiophenol with 4-(2-furyl)-3-nitrobut-3-en-2-one **1** (for its preparation see ref. 7). The reaction proceeds under the same conditions as that with *gem*-acetylnitrostyrenes (MeOH, 18–20 °C, 30 min). However, not a 2,3-dihydro- but 2,5-dihydro-1,5-benzothiazepine **2** is formed,[†] probably due to isomerization of the initial 2,3-dihydro-1,5-benzothiazepine to a more energetically favourable 2,5-dihydro one containing a nitroenamine moiety.



1, **2** R = 2-furyl
3, **4** R = 4-MeOC$_6$H$_4$

Scheme 1

In the case of 2-(4-methoxyphenyl)-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepine **3** obtained previously,[5,6] we succeeded to perform its prototropic conversion (by refluxing its methanolic solution for 3 h) to the 2,5-dihydro compound **4**.[‡] This confirms that benzothiazepine **2** is formed from the initially generated 2,3-dihydro form.

Note that sometimes,[8–15] the reactions of *gem*-substituted enones with *o*-aminothiophenol directly give 2,5-dihydro-1,5-benzothiazepines, in particular, those containing an alkoxycarbonyl or acetyl group at the C^3 atom.[8–13] In most cases, 2,5-dihydro deriva-

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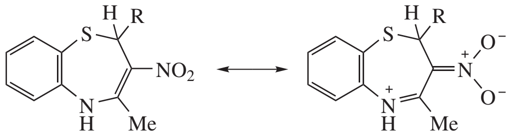
[†] *2-(2-Furyl)-4-methyl-3-nitro-2,5-dihydro-1,5-benzothiazepine* **2**. A solution of *o*-aminothiophenol (0.250 g, 2 mmol) in methanol (4 ml) was added to 4-(2-furyl)-3-nitrobut-3-en-2-one **1**[7] (0.362 g, 2 mmol). After 30 min, the reaction solution was poured into a Petri dish. The residue that remained after solvent evaporation was repeatedly treated with ethanol. Yield 0.394 g (68%), yellow crystals, mp 170–172 °C (ethanol). IR (ν/cm^{-1}): 1180–1290 (NOO$^-$), 1620 (C=C, C=N$^+$), 3410 (NH$^+$). ^{1}H NMR, δ: 2.75 (s, 3H, Me), 6.32 (s, 1H, C^{2}H), 6.65 (s, 1H, NH), 5.68 (d, 1H, H$^3_{\text{Fur}}$, ^3J 3.23 Hz), 5.94 (dd, 1H, H$^4_{\text{Fur}}$, ^3J 3.23, 1.86 Hz), 7.11 (d, 1H, H$^5_{\text{Fur}}$, ^3J 1.86 Hz), 6.90–7.00 (m), 7.14–7.22 (m, C$_6$H$_4$). ^{13}C{^{1}H} NMR, δ: 27.94 (Me), 44.98 (C^2), 128.24 (C^3), 150.78 (C^4), 108.44 (C$^3_{\text{Fur}}$), 109.87 (C$^4_{\text{Fur}}$), 142.27 (C$^5_{\text{Fur}}$), 151.36 (C$^2_{\text{Fur}}$), 122.10, 125.51, 125.71, 128.99, 134.83, 142.65 (C$_6$H$_4$). Found (%): C, 58.31; H, 4.31. Calc. for C$_{14}$H$_{12}$N$_2$O$_3$S (%): C, 58.33; H, 4.17.

[‡] *2-(4-Methoxyphenyl)-4-methyl-3-nitro-2,5-dihydro-1,5-benzothiazepine* **4**. A suspension of 2-(4-methoxyphenyl)-4-methyl-3-nitro-2,3-dihydro-1,5-benzothiazepine **3**[6] (0.220 g, 0.67 mmol) in methanol (10 ml) was refluxed for 3 h. The precipitate gradually appeared in solution, while the colouring intensity increased. The reaction mixture was poured into a Petri dish and the residue after solvent evaporation was treated with ethanol. Yield 0.121 g (55%), yellow crystals, mp 146–148 °C (ethanol). IR (ν/cm^{-1}): 1180–1290 (NOO$^-$), 1605 (C=C, C=N$^+$), 3410 (NH$^+$). ^{1}H NMR, δ: 2.75 (s, 3H, Me), 3.65 (s, 3H, OMe), 6.23 (s, 1H, C^{2}H), 6.68 (s, 1H, NH), 6.56, 6.92 (2d, 4H, OC$_6$H$_4$, ^3J 8.54 Hz), 6.80–6.91 (m, 2H, C$_6$H$_4$), 6.96 (m, 1H, C$_6$H$_4$), 7.11 (m, 1H, C$_6$H$_4$). ^{13}C{^{1}H} NMR, δ: 27.68 (Me), 50.52 (C^2), 55.23 (OMe), 129.36 (C^3), 150.94 (C^4), 113.37, 122.10, 125.43, 125.89, 128.44, 128.88, 131.95, 135.13, 143.05, 158.29 (2C$_6$H$_4$). Found (%): N, 8.33. Calc. for C$_{17}$H$_{16}$N$_2$O$_3$S (%): N, 8.54.

tives are generated on heating.[8–12] In case of alkoxycarbonyl-containing benzothiazepines 2,5 $\rightleftarrows$ 2,3-dihydro tautomerism was discovered.[12] However, for compounds **2**, **4** such a tautomerism was not observed, which could be due to greater –M-effect of nitro group compared to an ester one.

The composition and structure of the new compounds **2** and **4** were confirmed by elemental analyses, IR, electronic and NMR (^{1}H, ^{13}C, HMQC, HMBC) spectroscopic data.[§] Their IR spectra do not contain characteristic bands of the covalent nitro group, but exhibit intense bands of ionized nitro group in the range of 1180–1290 cm^{-1} as well as a set of C=C and C=N$^+$ double bonds at 1605–1620 cm^{-1}. This indicates a high polarization of molecules involving vicinal nitro and amino groups and a considerable contribution of bipolar forms to their electronic structure. The electronic spectra of 2,5-dihydro-1,5-benzothiazepines **2**, **4** contain long-wave absorption bands at 386 nm (ε 12950) and 390 nm (ε 10550), respectively, that are typical of nitroenamine systems.[16]



The methine protons of compounds **2**, **4** resonate in the ^{1}H NMR spectra (CDCl$_3$) as singlets at δ 6.32 and 6.23 ppm, while signals at δ 6.65 and 6.68 ppm belong to the protons of the NH groups.

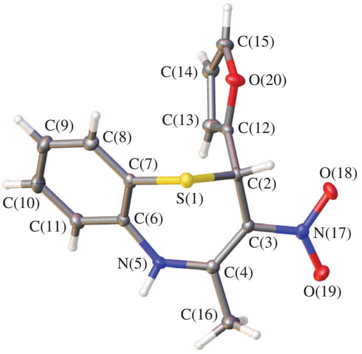


Figure 1 General view of molecule **2** with atoms represented as thermal vibration ellipsoids at 50% probability.

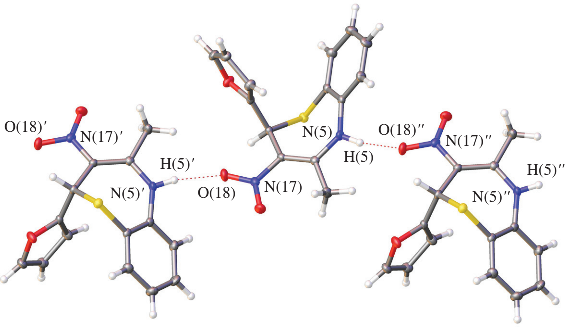


Figure 2 Coordination of compound **2** molecules by formation of intermolecular hydrogen bonds.

The structure of product **2** was ultimately established by X-ray diffraction study (Figures 1, 2).[¶] Seven-membered heterocycle in a molecule had a slightly distorted boat conformation, with the S(1) and C(6) atoms deviating from the plane by 1.088(2) and 0.440(2) Å, respectively. The structure of the nitroenamine moiety is nearly planar, with deviation from the plane not exceeding 12° [torsion angles: N(17)–C(3)–C(4)–N(5) –167.98(15)°, H(5)–N(5)–C(4)–C(3) –172.88(15)°, C(4)–C(3)–N(17)–O(18) 172.47(14)°, C(4)–C(3)–N(17)–O(18) –6.4(2)°]. This geometry results in efficient conjugation, so the C(4)–N(5) [1.352(2) Å], C(3)–N(17) [1.416(2) Å] bonds become shorter and the C(3)–C(4) [1.391(2) Å] bond elongates. In contrast, the C=C and C–NO$_2$ bond lengths in the molecules of nitroethene[17] and 1-methoxycarbonyl-1-nitro-2-phenylethene[18] containing no amino groups are 1.337, 1.331 Å and 1.470, 1.475 Å, respectively. Note that in molecules of the model compound, *E*-2-methylamino-1-nitroethene,[22] the trend in the variation of the bond lengths examined is the same as in our sample, namely, C–NH [1.303(7) Å], C–NO$_2$ [1.378(6) Å], C=C [1.356(7) Å].

Analogous trends in the variation of these parameters are observed in the structures of open-chain compounds with *cis*-orientation of arylamino and nitro groups, namely, in the 1-bromo-1-nitro-2-piperidino-2-phenylethene[23] and 3-bromo-2-(4-bromoanilino)-3-nitroacrylate[24] molecules. Data of X-ray diffraction analysis for two other substituted 2,5-dihydro-1,5-benzothiazepines containing no nitro groups were reported.[10,25] In fact, the seven-membered heterocycle in 2,4-diphenyl-3-(1,2,4-triazol-1-yl)-2,5-dihydro-1,5-benzothiazepine[25] is turned in another direction [C(4)–N(5) 1.394(4) Å, C(3)–C(4) 1.339(4) Å], while the geometries of fluorine-substituted ethyl 4-methyl-2-(4-fluorophenyl)-2,5-dihydro-1,5-benzothiazepine-3-carboxylate [C(4)–N(5) 1.379(3) Å, C(3)–C(4) 1.367(4) Å][10] and compound **2** are similar.

The molecules of compound **2** in a crystal are associated to give chains arranged along axis *b* (Figure 2) due to a set of hydrogen bonds [N(5)–H(5)···O(18)″ 2.053(1) Å] between the adjacent molecules. The chains are held together in a three-dimensional structure (Figure 3) by van der Waals interactions directed along axis *a* [the shortest contacts between atoms of adjacent molecules are C(10)–H(10)···O(20) 2.539(1) Å, C(14)–H(14)···O(19) 2.616(1) Å and C(11)–H(11)···O(18) 2.706(1) Å].

In summary, a convenient access to 2-(2-furyl)-4-methyl-3-nitro-2,5-dihydro-1,5-benzothiazepine has been developed. Similar compounds can be of interest as potential biologically

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[§] Physico-chemical studies were performed in the Center for Collective Use at A. I. Herzen State Pedagogical University of Russia. ^{1}H, ^{13}C{^{1}H} NMR, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC spectra were recorded with a Jeol JNM ECX400A spectrometer operating at 399.78 (^{1}H) and 100.53 MHz (^{13}C) in CDCl$_3$ solution; the signals of the residual nondeuterated solvents were used as internal standard. IR spectra were recorded with a Shimadzu IR-Prestige-21 Fourier spectrometer in chloroform (c = 40 mg ml^{-1}). Electronic absorption spectra were recorded with a Shimadzu UV2401PC spectrophotometer in ethanol solution in quartz cuvettes (l = 1.01 mm) at 0.5–0.8 mM. Elemental analysis was performed with an Eurovector EA 3000 (CHN Dual mode) analyzer.

[¶] For single crystal X-ray diffraction experiment, crystal of **2** was fixed on a micro mount, placed in an Agilent Technologies Excalibur diffractometer equipped with an EOS CCD detector and measured at a temperature of 100 K using monochromated MoKα radiation. The unit cell parameters [space group $C2/c$, a = 9.4605(3), b = 13.9936(3) and c = 20.2494(5) Å, β = 100.523(3)°, Z = 8] were refined by least square techniques using 6307 reflections in the 2θ range of 5.26–54.98°. The structure was solved by the direct methods and refined $R_1 = 0.036$ ($wR_2 = 0.076$) for 2501 unique reflections with $|F_0| \geqslant 4\sigma_F$ by means of the SHELXL–97 program[19] incorporated in the OLEX2 program package.[20] The carbon and nitrogen-bound H atoms were placed in calculated positions and were included in the refinement in the 'riding' model approximation, with U_{iso}(H) set to 1.5U_{eq}(C) and C–H 0.96 Å for Me groups, U_{iso}(H) set to 1.2U_{eq}(C) and C–H 0.93 Å for the CH groups, U_{iso}(H) set to 1.2U_{eq}(C) and C–H 0.98 Å for the tertiary CH groups and U_{iso}(H) set to 1.2U_{eq}(N) and N–H 0.86 Å for the NH groups. Empirical absorption correction was applied in CrysAlisPro[21] program complex using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

CCDC 1001599 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2014.

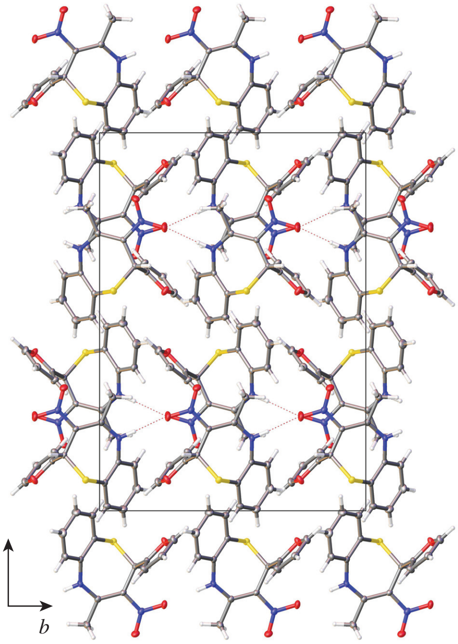

Figure 3 Packing of compound **2** molecules in a crystal.

active compounds and can be recommended for primary pharmacological tests.

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References

1 M. D. Mashkovskii, *Lekarstvennye sredstva (Drugs)*, Novaya Volna, Moscow, 2012 (in Russian).

2 M. Chaffman and R. N. Brogden, *Drugs*, 1985, **29**, 387.

3 V. G. Granik, *Lekarstva (Drugs)*, Vuzovskaya Kniga, Moscow, 2006 (in Russian).

4 M. D. Mashkovskii, *Lekarstva XXI veka (Drugs of XXI Century)*, Novaya Volna, Moscow, 1998 (in Russian).

5 R. I. Baichurin, N. I. Aboskalova and V. M. Berestovitskaya, *Russ. J. Org. Chem.*, 2010, **46**, 1590 (*Zh. Org. Khim.*, 2010, **46**, 1583).

6 V. M. Berestovitskaya, R. I. Baichurin, N. I. Aboskalova, K. A. Lysenko and I. V. Anan'ev, *Russ. J. Gen. Chem.*, 2011, **81**, 1163 (*Zh. Obshch. Khim.*, 2011, **81**, 970).

7 V. M. Berestovitskaya, N. I. Aboskalova, E. A. Ishmaeva, S. V. Bakhareva, G. A. Berkova, Ya. A. Vereshchagina, A. V. Fel'gendler and G. R. Fattakhova, *Russ. J. Gen. Chem.*, 2001, **71**, 1942 (*Zh. Obshch. Khim.*, 2001, **71**, 2049).

8 K. S. Atwal, J. L. Bergey, A. Hedberg and S. Moreland, *J. Med. Chem.*, 1987, **30**, 635.

9 D. G. Schmidt and H. Zimmer, *J. Org. Chem.*, 1983, **48**, 4367.

10 W. Li, J. Lan, C. Li, Y. Cao, H. Wang, L. Wang, P. Zhang, Y. Wang and Y. Li, *Acta Chimica Sinica (Huaxue Xuebao)*, 2009, **67**, 2732 (in Chinese) (*Chem. Abstr.*, 2010, **152**, 525825).

11 K. Tian, X. Liu, Z. Xue, T. Yang, X. Du and P. Zhang, *Chin. J. Org. Chem. (Youji Huaxue)*, 2013, **33**, 2237 (in Chinese) (*Chem. Abstr*., 2014, **161**, 55144).

12 Y. Wu, K. Tian, T. Yang, X. Du and P. Zhang, *Chin. J. Org. Chem. (Youji Huaxue)*, 2013, **33**, 1465 (in Chinese) (*Chem. Abstr*., 2013, **160**, 278894).

13 L. Wang, P. Zhang, X. Zhang, Y. Zhang, Y. Li and Y. Wang, *Eur. J. Med. Chem.*, 2009, **44**, 2815.

14 D.-B. Yang, F.-M. Liu, S.-Q. Shen and S.-W. Chen, *Chin. J. Org. Chem. (Youji Huaxue)*, 2010, **30**, 244 (in Chinese) (*Chem. Abstr*., 2010, **153**, 11631).

15 S.-Q. Chen, F. Ding and F.-M. Liu, *Phosphorus Sulfur Silicon Relat. Elem.*, 2011, **186**, 574.

16 S. Rajappa, *Tetrahedron*, 1999, **55**, 7065.

17 H. D. Hess, A. Bauder and H. H. Günthard, *J. Mol. Spectrom*., 1967, **22**, 208.

18 V. G. Andrianov, Yu. T. Struchkov and K. K. Babievsky, *Cryst. Struct. Commun.*, 1982, **11**, 31.

19 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112.

20 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr*., 2009, **42**, 339.

21 *CrysAlisPro*, Agilent Technologies, Version 1.171.36.32 (release 02-08-2013).

22 E. N. Gate, M. A. Meek, C. H. Schwalbe, M. F. G. Stevens and M. D. Threadgill, *J. Chem. Soc., Perkin Trans. 2*, 1985, 251.

23 E. A. Ishmaeva, V. M. Berestovitskaya, I. A. Litvinov, Ya. A. Vereshchagina, E. G. Yarkova, G. R. Fattakhova, D. B. Krivolapov, S. V. Makarenko, E. V. Trukhin and I. V. Pavlova, *Russ. J. Gen. Chem.*, 2001, **71**, 429 (*Zh. Obshch. Khim.*, 2001, **71**, 466).

24 V. M. Berestovitskaya, S. V. Makarenko, K. S. Kovalenko, I. A. Litvinov, D. B. Krivolapov and A. D. Shevchenko, *Russ. J. Gen. Chem.*, 2011, **81**, 376 (*Zh. Obshch. Khim.*, 2011, **81**, 277).

25 S.-Q. Chen and F.-M. Liu, *J. Chem. Crystallogr*., 2011, **41**, 485.

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