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Unexpected transformations of 11-acetyl-8-bromo-2-methyl-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4(3*H*)-one(thione)

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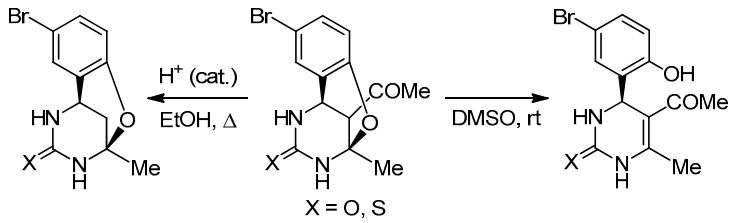


11-Acetyl-8-bromo-2-methyl-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4(3*H*)-one and -4(3*H*)-thione are prepared *via* the three-component Biginelli condensation as the only diastereomers. For the first time we observed that these compounds in DMSO solution undergo a slow isomerization with formation of mixtures with the respective 4-(5-bromo-2-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one(thione). The same methanobenzoxadiazocines underwent deacetylation in boiling ethanol in the presence of HCl.

Keywords: 11-acetyl-8-bromo-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4(3*H*)-one, 11-acetyl-8-bromo-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-4(3*H*)-thione, bromosalicylaldehyde, Biginelli reaction, deacetylation, intramolecular transformation.

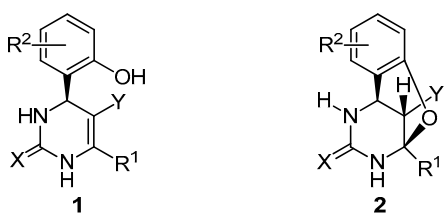
4-Aryl-3,4-dihydropyrimidin-2(1*H*)-ones and -4(3*H*)-thiones are Ca channel modulators and show various types of biological activity – antihypertensive, antiarrhythmic, antiviral, antibacterial, etc.[1] A certain interest is shown toward their structural analogs with a hydroxyaryl fragment and 5-carbonyl substituent in the dihydropyrimidine ring because of antineoplastic activity of these compounds.[1,2]

The synthesis of such structures is based on the three-component Biginelli cyclocondensation of β-dicarbonyl compounds, hydroxyaromatic aldehydes, and urea or thiourea.[3] The behavior of salicyl aldehydes in this reaction has ambiguous character and the cyclocondensation can lead not only to compounds **1** (Fig. 1), but also to dihydromethanobenzoxadiazocines **2**,[4,5] including acetyl derivatives.[6–9]

Such changes in the molecular structure of isomeric carbonyl compounds lead to alternate types of biological activity. It is thus shown that the *O*-bridged derivative **2** (R^1 = Me, R^2 = OMe, X = O, Y = COMe) has a pronounced antihypertensive action.[10] It is obvious that similar biologically active molecules with distinct spatial structures, such as **1** and **2**, may exhibit different selectivity of interaction with the corresponding bioreceptors and other structures of the cell.

Our interest was turned toward studying of the peculiarities of *O*-bridged structures **2** in comparison with structures of ordinary Biginelli products **1**. During the work we have paid attention to a spontaneous isomerization of some 11-acetyl-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocinones, which slowly proceeds in neutral DMSO solution at ambient temperature with the formation of the corresponding 5-acetyl-4-(2-hydroxyaryl)-3,4-dihydropyrimidin-2(1*H*)-ones. It should be noted that until now such transformation of 5-carbonylmethanobenzoxadiazocinones was observed only when they were heated in ethanol in the presence of an acid catalyst.[4c]

The most convenient compounds for studying of intramolecular transformations appeared to be bromo-substituted *O*-bridged structures, such as 11-acetyl-8-bromo-2-methyl-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4-(3*H*)-one (**3**) and the corresponding thione **4** (Scheme 1).

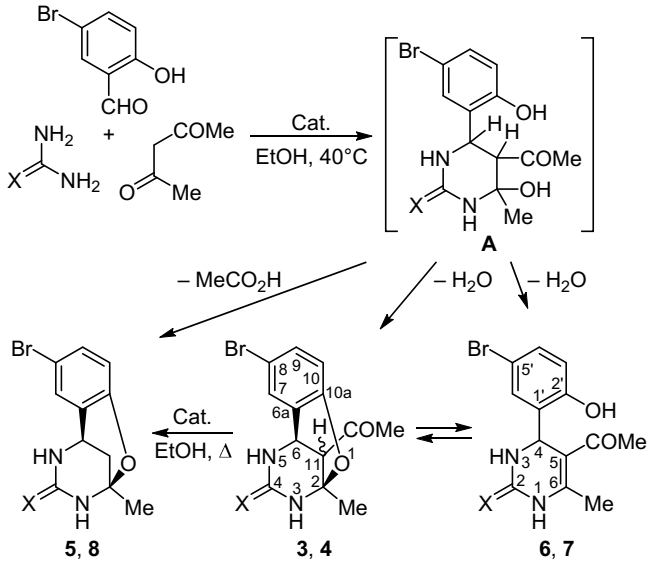


1 **2**

R^1 = Me, Ph, etc.; R^2 = H, Me, Br, OH, OMe, NO_2, etc; X = O, S; Y = COAlk, COAr, COOAlk, $CONR_2$

Figure 1. Reaction products **1** and **2** of the Biginelli cyclocondensation with salicyl aldehydes.

Scheme 1



The synthesis of compounds was carried out with the use of acetylacetone, 5-bromosalicylaldehyde, urea or thiourea as starting materials and an acid catalyst (Scheme 1).

The variation of temperature and acidity of the reaction medium allowed to choose the experimental conditions for preparation of compounds **3** and **4**, pure enough for subsequent experiments. These compounds were obtained when carrying out the reaction at 40°C in ethanol in moderate presence of concd HCl or $NaHSO_4$ as catalyst (Scheme 1). Methanobenzoxadiazocinethione **4** was isolated from the reaction mixture as individual compound with the yield of 48% (catalyst HCl) and 68% (catalyst $NaHSO_4$) irrespective of the reaction time (3–9 h).

The product isolated from the reaction of 5-bromosalicylaldehyde, acetylacetone, and urea represented a mixture of two compounds **3** and **5**. It was established that the molar ratio of these compounds in the product depends on the time of carrying out the cyclization. Thus, within 3 h, only compound **3** was formed, while the prolongation of the reaction time to 9 h produced the mixture of compounds **3** and **5** with the total yield of 52% (the compound ratio of 92:8, catalyst HCl) and 64% (the ratio of 95:5, catalyst $NaHSO_4$). The non-bridged isomeric compound **6** was not detected in the isolated reaction products. It is significant that the amount of compound **3** and its isomer **6** in the reaction mixture became nearly equal (52 and 44%, respectively), along with a minor part of compound **5** (4%), when the amount of HCl catalyst was doubled. These facts allow to consider kinetically controlled formation of the bridged structure **3** as the main path of the Biginelli reaction at 40°C.

The formation of dihydropyrimidinone **6** is due to a rupture of the C(2)–O(1) bond in methanobenzoxadiazocine **3** (retro-oxa-Michael reaction). At the same time, the side process of deacetylation with elimination of molecule of acetic acid from the assumed intermediate **A** and formation of compound **5**, but also process of direct formation of hydroxyaryl dihydropyrimidinone **6** with elimination of a molecule of water can proceed in a slight degree. It is clear, that these both processes happen under an acidic conditions with the participation of the corresponding carbocation. These observations disprove the idea of primary formation of dihydropyrimidinones **6**, **7** which subsequently undergo the oxa-Michael reaction to form *O*-bridged structures.[5,7]

The structures of isolated compounds **3**–**5** are confirmed by the elemental analysis, mass spectra, ^{1}H and ^{13}C NMR spectra.[8,10,11] In the IR spectra of these compounds, the characteristic bands are observed at 1692–1695 cm^{-1} (amide C=O)[7] for compounds **3**, **5** and 1566 cm^{-1} (C=S)[12] for compound **4**, besides of the band of acetyl group carbonyl at 1718−1720 cm^{-1} for compounds **3** and **4**. The NMR data for compounds **6** and **7** are in accordance with the data for corresponding debromo analogs.[13,14]

The minor compound **5** revealed the characteristic signal of two geminal atoms of the 11-CH_2 group at 2.06 and 2.14 ppm (^2J = 12.8 Hz) and double doublet of the vicinal 6-CH atom at 4.28 ppm in the ^{1}H NMR spectrum, as well as the characteristic signal of the C-2 atom at 82.8 ppm in ^{13}C NMR spectrum. This is evidence for the structure of methanobenzoxadiazocinone without acetyl group at position 11 (Scheme 1).[15]

Compound **5** was prepared with the yield of 56% in the special experiment of cyclocondensation carried out in boiling ethanol and also when compound **3** was boiled in ethanol in the presence of HCl.

We showed that product **8** also is formed upon heating compound **4** in refluxing ethanol in the presence of HCl. There are no communications on the acetyl group extrusion in the Biginelli reaction. The preparation of compound **5** and other similar 11-unsubstituted benzoxadiazocinones (-thiones) was earlier performed through the decarboxylation of corresponding acid derivatives[15,16] or by direct cyclocondensation of acetone, salicyl aldehyde, and urea (or thiourea).[17]

The very slow transformation of compound **3** into compound **6** in solution has been noted above. We studied the behavior of the mixtures of compounds **3** + **5** in DMSO-d_6 solution at room temperature by the NMR spectra (Table 1). The reaction products are stable in this solution for about two days, but then there appear the weak signals of 3,4-dihydropyrimidinone **6** (Fig. 2). This compound featured a characteristic doublet signal of the 4-CH proton at 5.50 ppm. The concentration of compound **6** in DMSO solution slowly increases and in 150 days reaches 61%.

The behavior of methanobenzoxadiazocinethione **4** in DMSO solution was similar. After three days of keeping of this sample in DMSO-d_6 at room temperature, the signals that belong to 3,4-dihydropyrimidine-2(1*H*)-thione (**7**)

Table 1. Composition of the reaction products and change of the product ratio with time*

Products	Initial ratio	In DMSO-d_6 solution			In precipitate from DMSO–H_2O, 1:10
3 + **5** + **6**	92:8:0	10 days 89:8:3	50 days 84:8:8	150 days 31:8:61	24:8:68
4 + **7**	100:0	3 days 92:8	40 days 85:15	120 days 72:28	74:26

* From relative intensities of the ^{1}H NMR signals of 6-CH (~4.5 ppm) for compounds **3**, **4**, **5** and 4-CH (~5.5 ppm) for compounds **6**, **7**.

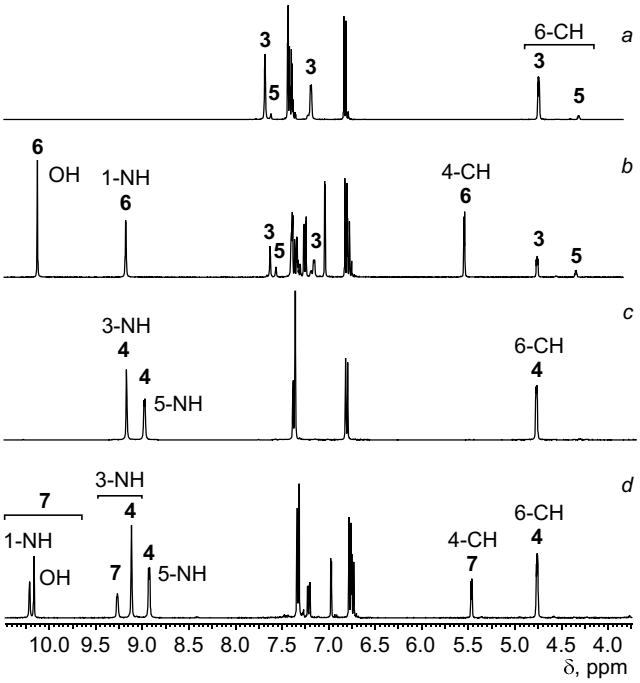


Figure 2. Fragments of the ^{1}H NMR spectra of compounds **3**–**7** in DMSO-d_6. The compounds ratio in the mixture: *a*) **3** + **5** (92:8); *b*) **3** + **5** + **6** (31:8:61, after 150 days); *c*) **4**; *d*) **4** + **7** (72:28, after 120 days). For numbering the protons, see Scheme 1.

appear in NMR spectra. Subsequently, the quantity of compound **7** slowly increases in solution and in 4 months reaches 28% (Fig. 2).

After the precipitation of the product mixture **3** + **5** + **6** by diluting the DMSO solution with water, the ratio of the compounds became 24:8:68 that implies continuation of slow course of the retro-oxa-Michael reaction of compound **3**. At the same time we did not observe noticeable change of the mixture of acetylthiones **4** and **7** in DMSO after dilution with water (Table 1).

In summary, we have demonstrated for the first time a transformation of 5-acetyl derivatives of dihydromethano-benzoxadiazocinones(thiones) in DMSO solution with the formation of mixtures with the corresponding 2-hydroxy-phenyldihydropyrimidinones(thiones). The observations indicate a relative instability of an oxadiazocine cycle in the structures of acetyl derivatives under the action of dipolar aprotic solvents.

Experimental

IR spectra were recorded on a Bruker Vector 22 spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, using residual solvent peaks 2.50 ppm (^{1}H) and 39.5 ppm (^{13}C) as internal standard. The signal assignments were based on the literature data[8,10,11] and also were verified by standard methods involving the acquisition of ^{13}C spectra in J-modulation mode (J-MOD). Mass spectra were recorded on a DFS Thermo Electron Corporation spectrometer (EI, 70 eV), the *m*/*z* values are given for the ^{79}Br, ^{32}S isotopic components. Elemental analysis was carried out with an EuroVector EA300 analyzer. Analysis of Br and S was performed by titrimetric method.

Three-component Biginelli condensation (General method). A mixture of acetylacetone (0.6 g, 6 mmol), 5-bromosalicylaldehyde (1.2 g, 6 mmol), urea (0.5 g, 9 mmol) or thiourea (0.7 g, 9 mmol), ethanol (5 ml), and 2 drops of concd aqueous HCl was stirred at 40°C for 9 h. The reaction mixture was cooled, and the precipitate was filtered off, washed with water and ethanol, dried, and crystallized from ethanol.

11-Acetyl-8-bromo-2-methyl-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4(3*H*)-one (3). Yield 1.0 g (52%), contains compound **5** as impurity, mp 260–264°C (mp 287–289°C[8]). IR spectrum, ν, cm^{-1}: 3254 (NH), 3115, 2904, 1720 (C=O), 1692 (NH−C=O), 1504, 1477, 1246. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.64 (3H, s, CH_3); 2.27 (3H, s, CH_3CO); 3.35–3.41 (1H, m, 11-CH); 4.70 (1H, dd, *J* = 4.5, *J* = 2.6, 6-CH); 6.77 (1H, d, *J* = 8.6, H-10); 7.13 (1H, d, *J* = 4.3, 5-NH); 7.34 (1H, dd, *J* = 8.6, *J* = 2.7, H-9); 7.37 (1H, d, *J* = 2.4, H-7); 7.62 (1H, s, 3-NH). ^{13}C NMR spectrum, δ, ppm: 23.4 (CH_3); 28.9 ($\underline{C}H_3CO$); 46.4 (C-6); 49.3 (C-11); 83.8 (C-2); 111.3 (C-8); 119.0 (C-10); 128.3 (C-6a); 131.2 (C-9); 131.8 (C-7); 150.2 (C-10a); 154.6 (C-4); 203.6 ($CH_3\underline{C}$=O). Mass spectrum, *m*/*z* (I_{rel}, %): 324 $[M]^+$ (33), 307 $[M-OH]^+$ (70), 281 $[M-COCH_3]^+$ (39), 153 $[C_7H_9N_2O_2]^+$ (100). Found, *m*/*z*: 324.0105 $[M]^+$. $C_{13}H_{13}BrN_2O_3$. Calculated, *m*/*z*: 324.0104. Found, %: Br 24.50; N 8.39. $C_{13}H_{13}BrN_2O_3$. Calculated, %: Br 24.58; N 8.62.

11-Acetyl-8-bromo-2-methyl-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-4(3*H*)-thione (4). Yield 1.0 g (48%), mp 233–235°C (mp 187−188°C,[6] mp 221–222°C,[11] mp 255–257°C[8]). IR spectrum, ν, cm^{-1}: 3354, 3236 (NH), 3145, 3070, 2956, 1718 (C=O), 1566 (NH−C=S), 1510, 1238. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.68 (3H, s, CH_3); 2.27 (3H, s, CH_3CO); 3.44 (1H, br. s, 11-CH); 4.80 (1H, dd, *J* = 5.0, *J* = 2.1, 6-CH); 6.82 (1H, d, *J* = 8.3, H-10); 7.36–7.39 (2H, m, H-7,9); 8.97 (1H, d, *J* = 4.7, 5-NH); 9.15 (1H, s, 3-NH). ^{13}C NMR spectrum, δ, ppm: 22.6 (CH_3); 29.1 ($\underline{C}H_3CO$); 46.9 (C-6); 47.5 (C-11); 82.0 (C-2); 111.6 (C-8); 118.8 (C-10); 126.6 (C-6a); 131.3 (C-9); 132.1 (C-7); 150.0 (C-10a); 176.8 (C-4); 203.1 ($CH_3\underline{C}$=O). Found, %: Br 23.11; N 8.26; S 9.56. $C_{13}H_{13}BrN_2O_2S$. Calculated, %: Br 23.42; N 8.21; S 9.40.

8-Bromo-2-methyl-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4(3*H*)-one (5). Method I. The mixture of acetylacetone (1.0 g, 10 mmol), 5-bromosalicylaldehyde (1.6 g, 8 mmol), urea (0.5 g, 8 mmol), concd HCl (0.1 ml), and ethanol (5 ml) was refluxed for 3 h. The mixture was cooled, and the precipitate was filtered off, washed with water, ethanol, and crystallized from ethanol. Yield 1.27 g (56%), mp 295−298°C (mp 293−296°C[15]). IR spectrum, ν, cm^{-1}: 3232 (NH), 3105, 2997, 2939, 1695 (NH−C=O), 1508, 1305, 1255. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60 (3H, s, CH_3); 2.06 (1H, d, *J* = 12.8) and 2.14 (1H, dd, *J* = 12.8, *J* = 3.0, 11-CH_2); 4.28 (1H, dd, *J* = 7.1, *J* = 3.0, 6-CH); 6.74 (1H, d, *J* = 8.2, H-10); 7.16 (1H, br. s, 5-NH); 7.31 (1H, dd, *J* = 8.2, *J* = 2.4, H-9); 7.32 (1H, s, H-7); 7.56 (1H, s, 3-NH). ^{13}C NMR spectrum, δ, ppm: 26.2 (CH_3); 31.7 (C-11); 44.2 (C-6); 82.8 (C-2); 111.1 (C-8); 118.9 (C-10); 128.2 (C-6a); 131.3 (C-9); 131.4 (C-7); 150.9 (C-10a); 155.1 (C-4). Mass spectrum, *m*/*z* (I_{rel},%): 282 $[M]^+$ (40), 267 $[M-15]^+$ (75), 111 $[C_5H_7N_2O]^+$ (100). Found, *m*/*z*:

281.9993 $[M]^+$. $C_{11}H_{11}BrN_2O_2$. Calculated, *m*/*z*: 281.9998. Found, %: C 46.73; H 3.40; Br 28.38; N 9.87. $C_{11}H_{11}BrN_2O_2$. Calculated, %: C 46.66; H 3.92; Br 28.23; N 9.90.

Method II. A solution of compound **3** (2.3 g, 7 mmol) and 5 drops of concd HCl in EtOH (10 ml) was refluxed for 1.5 h. The mixture was cooled, and the precipitate was filtered off, washed with water, EtOH, and crystallized from EtOH. Yield 1.2 g (60%), mp 297−298°C.

5-Acetyl-4-(5-bromo-2-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (6) was formed in DMSO-d_6 solution of benzoxadiazocine **3** in the NMR ampoule at room temperature over 5 months (61% in the mixture). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.07 (3H, s, CH_3); 2.28 (3H, s, CH_3CO); 5.50 (1H, d, *J* = 3.2, 4-CH); 6.79 (1H, d, *J* = 8.6, H-3'); 7.02 (1H, d, *J* = 2.4, H-6'); 7.24 (1H, dd, *J* = 8.6, *J* = 2.4, H-4'); 7.39 (1H, br. s, 3-NH); 9.20 (1H, s, 1-NH); 10.17 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 18.7 (CH_3); 29.8 ($\underline{C}H_3CO$); 48.7 (C-4); 107.9 (C-5); 110.2 (C-5'); 117.9 (C-3'); 129.5 (C-4'); 131.2 (C-6'); 132.4 (C-1'); 148.4 (C-6); 152.1 (C-2); 153.7 (C-2 Ar); 194.6 ($CH_3\underline{C}$=O).

5-Acetyl-4-(5-bromo-2-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (7) was formed in DMSO-d_6 solution of benzoxadiazocine **4** in the NMR ampoule at room temperature over 4 months (27% in the mixture). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.13 (3H, s, CH_3); 2.28 (3H, br. s, CH_3CO); 5.52 (1H, d, *J* = 3.5, 4-CH); 6.79 (1H, d, *J* = 8.6, H-3'); 7.02 (1H, d, *J* = 2.7, H-6'); 7.26 (1H, dd, *J* = 8.6, *J* = 2.7, H-4'); 9.32 (1H, s, 3-NH); 10.21 (1H, s, 1-NH (OH)); 10.26 (1H, s, OH (1-NH)). ^{13}C NMR spectrum, δ, ppm: 18.0 (CH_3); 29.9 ($\underline{C}H_3CO$); 49.2 (C-4); 109.3 (C-5); 110.2 (C-5'); 118.0 (C-3'); 130.0 (C-4'); 131.2 (C-1'); 131.6 (C-6'); 144.1 (C-6); 153.8 (C-2 Ar); 174.3 (C-2); 195.3 ($CH_3\underline{C}$=O).

8-Bromo-2-methyl-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-4(3*H*)-thione (8) was prepared from acetyl derivative **4** (2.4 g, 7 mmol) by analogy with compound **5** (method II). Yield 2.0 g (95 %), mp 294−296°C (mp 255−257°C[8]). IR spectrum, ν, cm^{-1}: 3172 (NH), 3103, 2968, 1570 (NH−C=S), 1518, 1471, 1246. ^{1}H NMR spectrum, δ, ppm (*J,* Hz): 1.66 (3H, s, CH_3); 2.10 (2H, br. s, 11-CH_2); 4.36–4.45 (1H, m, 6-CH); 6.79 (1H, d, *J* = 8.6, H-10); 7.25–7.40 (2H, m, H-7,9); 9.02 (1H, d, *J* = 3.4, 5-NH); 9.11 (1H, s, 3-NH). ^{13}C NMR spectrum, δ, ppm: 25.3 (CH_3); 29.9 (C-11); 44.7 (C-6); 81.1 (C-2); 111.5 (C-8); 118.9 (C-10); 126.4 (C-6a); 131.4 (C-9); 131.8 (C-7); 150.7 (C-10a); 176.4 (C-4). Mass spectrum, *m*/*z* ($I_{rel.}$,%): 298 $[M]^+$ (100), 283 $[M-15]^+$ (21). Found, *m*/*z*: 297.9767 $[M]^+$. $C_{11}H_{11}BrN_2OS$. Calculated, *m*/*z*: 297.9770. Found, %: C 44.21; H 3.66; Br 27.02; N 9.40; S 10.71. $C_{11}H_{11}BrN_2OS$. Calculated, %: C 44.16; H 3.71; Br 26.71; N 9.36; S 10.72.

Isomerization of benzoxadiazocines in solution (General method). A solution of benzoxadiazocine **3** (in a mixture with compound **5** (92:8)) or **4** (30 mg) in DMSO-d_6 (0.5 ml), which was colorless at the moment of dissolution, acquired yellow color upon keeping at ~20°C. ^{1}H NMR spectra of each sample were regularly recorded while changes were observed in solutions until the spectra of the mixtures showed a constant ratio of isomers, indicating that an equilibrium was reached (see Table 1). This solution was poured into water (5 ml). A precipitate was slowly formed upon standing. Usually, a solution was allowed to stand for several days to maximize amount of isolated precipitate. The precipitate (80–85% based on the starting weight) was filtered off, washed with water, and dried. Then the precipitate was dissolved in DMSO-d_6 to record ^{1}H NMR spectrum.

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Mass spectra, IR and NMR spectra were recorded at the Chemical Service Center of the SB RAS.

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