



# INTERACTION OF NINHYDRIN WITH *N*-HYDROXYUREA AND *N*-ALKOXYUREAS IN ACETIC ACID

Vasiliy G. Shtamburg,<sup>[a]\*</sup> Victor V. Shtamburg,<sup>[a]</sup> Andrey A. Anishchenko,<sup>[b]</sup> Svitlana V. Shishkina,<sup>[c]</sup> Irina S. Konovalova<sup>[c]</sup> and Alexander V. Mazepa<sup>[d]</sup>

**Keywords:** Ninhydrin, *N*-hydroxyurea, *N*-alkoxyureas, synthesis, structure, C–C bond elongation.

We have found that ninhydrin reacted with *N*-hydroxyurea and *N*-alkoxyureas in acetic acid with the predominant formation of diastereomers of 1,3a,8a-trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione and 1-alkoxy-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones, respectively. with *sic*-orientation of 3a,8a-HO-groups. The X-ray structural analysis of 1,3a*S*,8a*R*-trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione and 1-*n*-butyloxy-3a*S*,8a*R*-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione has demonstrated their specific structural features.

## \* Corresponding Authors

Phone: +380-97-651-61-72

E-Mail: stamburg@gmail.com

[a] 49005 Ukraine, Dnepr, Gagarina st., 8. Ukrainian State University of Chemical Technology.

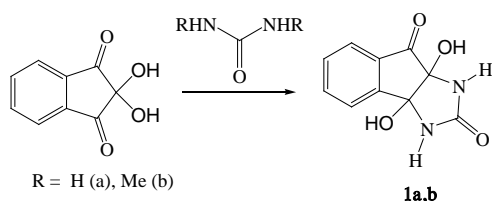
[b] 49050 Ukraine, Dnepr, Nauchnaya st. 25. O. Gonchar Dnepropetrovsk National University.

[c] 61001 Ukraine, Kharkov, Science ave., 60. SSI "Institute for Single Crystals", National Academy of Sciences of Ukraine.

[d] 65080 Odessa, Luystdorskaya Doroga st., 86. A.V. Bogatsky Physico-Chemical Institute of NAS of Ukraine.

## INTRODUCTION

Nitrogen-containing heterocyclic systems, such as hydantoin and imidazolidin-2-ones, are common in pharmaceutical materials. It is therefore important to create the reaction strategies that give access to such biologically active synthones. As it is known,<sup>1-4</sup> ninhydrin (indane-1,2,3-trione hydrate) reacts with urea and *N,N'*-dimethylureas yielding 3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones (**1a,b**) (Scheme 1).

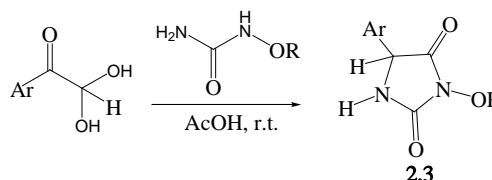


**Scheme 1.** Ninhydrin's interaction with the ureas.

Compounds **1a,b** were used as the essential intermediates in the diastereoselective synthesis of some dihydrofuran derivatives<sup>3</sup> and pharmaceuticals.<sup>3,5</sup>

The study of the vicinal polycarbonyl compounds interaction with *N*-hydroxyurea and its derivatives<sup>6-10</sup> has recently been started by our research group and needs to be continued. Derivatives of *N*-hydroxyurea are common in pharmaceuticals. But the ninhydrin's interaction with *N*-hydroxyurea and *N*-alkoxyureas has not been investigated in contrast to the arylglyoxal reactions with *N*-hydroxyurea and *N*-alkoxyureas.<sup>6-10</sup>

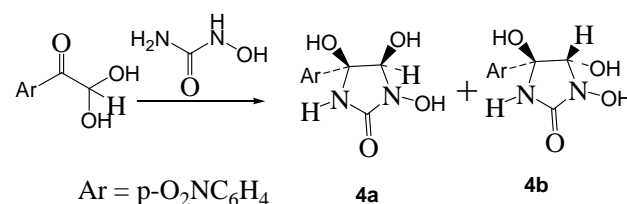
Earlier we have found<sup>8</sup> that most of arylglyoxals reacted with *N*-hydroxyurea and *N*-alkoxyureas in acetic acid producing 3-hydroxyhydantoin **2** and 3-alkoxyhydantoin **3** (Scheme 2).



Ar = *p*-XC<sub>6</sub>H<sub>4</sub>, X = H (a), F(b), Cl(c), Br(d)  
R = H(2), Me, Et, Bu(3)

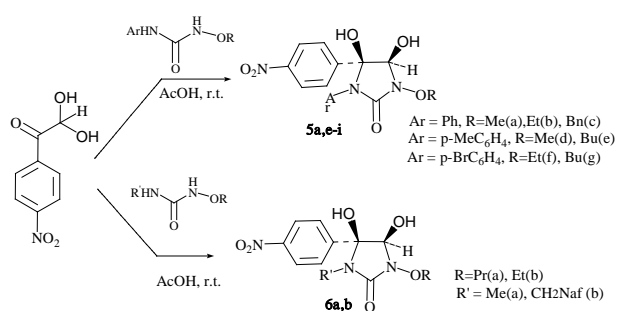
**Scheme 2.** Interaction of the most of arylglyoxals with *N*-hydroxyurea and *N*-alkoxyureas in the acetic acid.

In aqueous medium this reaction can have ambiguous results and the product's nature strongly depends on the nature of arylglyoxal.<sup>6</sup> 4-Nitrophenylglyoxal, however, reacts with *N*-hydroxyurea producing<sup>9</sup> the mixture of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones **4a** and **4b** in molar ratio approximately 3:1 (Scheme 3).



**Scheme 3.** Interaction of 4-nitrophenylglyoxal with *N*-hydroxyurea.

Moreover, 4-nitrophenylglyoxal diastereoselectively reacts with *N*-alkoxy-*N'*-arylsureas and *N*-alkoxy-*N'*-alkylureas in acetic acid at 17–20° C mainly producing 3-alkoxy-1-aryl-4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones **5** and 3-alkoxy-1-alkyl-4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones **6**.<sup>10</sup> These diastereomers **5,6** have *cis* orientation of 4-HO- and 5-HO-moieties (Scheme 4).



**Scheme 4.** Interaction of 4-nitrophenylglyoxal with *N*-alkoxy-*N'*-arylureas and *N*-alkoxy-*N'*-alkylureas.

Thus the goal of our present research is to investigate the interaction of ninhydrin with *N*-hydroxyurea and *N*-alkoxyureas in acetic acid medium.

## EXPERIMENTAL

<sup>1</sup>H NMR spectra were recorded on a Varian VXP-300 spectrometer (300 MHz). <sup>13</sup>C NMR spectra were recorded on a Varian VXP-300 spectrometer (75 MHz). The solvent DMSO-*d*<sub>6</sub> was used. <sup>1</sup>H NMR chemical shifts relative to the residual solvent protons as an internal standard [(CD<sub>3</sub>)<sub>2</sub>SO: 2.500 ppm] were reported. Solvent carbon atoms served as an internal standard for <sup>13</sup>C NMR spectra [(CD<sub>3</sub>)<sub>2</sub>SO: 39.52 ppm]. Mass spectra were recorded on a VG 70-70EQ mass spectrometer in fast atom bombardment mode (FAB). The solvents were purified and dried according to the standard procedures.

### 1,3a,8a-Trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (7)

**A.** *N*-Hydroxyurea (74.6 mg, 0.981 mmol) was dissolved in a solution of ninhydrin (145.6 mg, 0.817 mmol) in acetic acid (7 mL) by stirring at 16 °C. The reaction solution was maintained at 8 °C for 23 h, then it was heated to 16 °C, the obtained white precipitate was filtered out, dried under vacuum (3 mmHg) at 25 °C, washed with MeCN (2 mL) and dried under vacuum (3 mmHg), giving 190 mg (98 %) *cis*-3a,8a-dihydroxydiastereomer of **7**, colorless crystals, m. p. 169–171 °C (with decomp.), m. p. 172–174 °C (with decomp., THF–hexane). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ = 6.646 (1H, s, OH), 7.268 (1H, s, OH), 7.615 (1H, t, *J* = 7.5 Hz, Ar), 7.750 (1H, d, *J* = 7.2 Hz, Ar), 7.762 (1H, d, *J* = 7.2 Hz, Ar), 7.859 (1H, t, *J* = 7.5 Hz, Ar), 8.409 (1H, s, NH), 9.131 (1H, s, NOH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ = 84.33 (C–OH), 89.36 (C–OH), 123.44 [C(H) Ar], 124.92 [C(H) Ar], 130.46 [C(H) Ar], 132.28 [C<sub>q</sub> Ar], 136.53 [C(H) Ar], 150.82 [C<sub>q</sub> Ar], 156.05 [HN(C=O)NOH], 195.63 (C=O). MS (FAB) *m/z* 237 [M+H]<sup>+</sup> (90), 176 [M+H-H<sub>2</sub>O-HCNO]<sup>+</sup> (68), 90(57), 72(100). Anal. Calc. for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>5</sub>: C 50.85, H 3.41, N 11.86. Found: C 50.87, H 3.51, N 11.69.

**B.** Ninhydrin (149.1 mg, 0.837 mmol) was dissolved in the solution of *N*-hydroxyurea (71.6 mg, 0.941 mmol) in acetic acid (5 mL) by stirring at 20 °C for 3 h. The obtained white precipitate was filtered out, dried under vacuum (3 mmHg) at 25 °C, yielding 182.3 mg (92 %) of *cis*-3a,8a-

dihydroxydiastereomer **7**, colorless crystals, m. p. 169–171 °C (with decomp.).

### 1-Methoxy-3a*S*,8a*R*-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (8a)

**A.** Ninhydrin (150.3 mg, 0.844 mmol) was dissolved in the solution of *N*-methoxyurea (76 mg, 0.844 mmol) in acetic acid (6 mL) by stirring at 20 °C for 1 h. The reaction solution was maintained at 20 °C for 1 h, maintained at 5 °C for 20 h, then acetic acid was evaporated under vacuum (3 mmHg) at 18 °C, the residue was extracted with water (3 mL) at 5 °C. The obtained precipitate was filtered off, dried under vacuum (3 mmHg) giving 142 mg (67 %) of *cis*-3a,8a-dihydroxydiastereomer of **8a**, colorless crystals, m. p. 197–199 °C (with decomp., THF–hexane). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ = 3.598 (3H, s, NOME), 6.792 (1H, s, OH), 7.524 (1H, s, OH), 7.632 (1H, t, *J* = 7.5 Hz, Ar), 7.748 (1H, d, *J* = 7.5 Hz, Ar), 7.784 (1H, d, *J* = 7.5 Hz, Ar), 7.879 (1H, t, *J* = 7.5 Hz, Ar), 8.663 (1H, s, NH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 64.36 (NOME), 84.37 (C–OH), 88.92 (C–OH), 123.63 [C(H) Ar], 124.90 [C(H) Ar], 130.57 [C(H) Ar], 131.91 [C<sub>q</sub> Ar], 136.83 [C(H) Ar], 150.73 [C<sub>q</sub> Ar], 155.19 [N(C=O)N], 196.14 (C=O). MS (FAB) *m/z* 501(2M+H)<sup>+</sup> (10), 251 (M+H)<sup>+</sup> (100), 191 (30), 161 (16). Anal. Calc. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>: C 52.80, H 4.03, N 11.20. Found: C 52.82, H 4.03, N 11.14.

**B.** Ninhydrin (130 mg, 0.730 mmol) was dissolved in the solution of *N*-methoxyurea (66 mg, 0.730 mmol) in acetic acid (6 mL) by stirring at 19 °C for 1 h. The reaction mixture was maintained at 16 °C for 2 h, then acetic acid was evaporated under vacuum (3 mmHg) at 20 °C, giving 182 mg (99 %) of mixture of *cis*-3a,8a-dihydroxydiastereomer **8a** (89 %) and *trans*-3a,8a-dihydroxydiastereomer **8b** (11 %). This mixture was extracted by water (10 mL) at 4 °C for 25 h, the precipitate was filtered off, washed with water (5 mL), the combined aqueous filtrate was evaporated under vacuum (3 mmHg) at 20 °C, giving 91 mg (50 %) of **8a**.

### 1-Ethoxy-3a*S*,8a*R*-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (9a)

**A.** Ninhydrin (214.9 mg, 1.206 mmol) was dissolved in the solution of *N*-ethoxyurea (125.6 mg, 1.206 mmol) in acetic acid (6 mL) by stirring at 14 °C for 6 h, the reaction solution was maintained at 17 °C for 22 h, then it was frozen and acetic acid was evaporated under vacuum (3 mmHg). The obtained residue was washed with water (2 mL) at 5 °C, dried under vacuum (3 mmHg), giving 230 mg (72 %) of *cis*-3a,8a-dihydroxydiastereomer **9a**, colorless crystals, m. p. 161–163 °C (with decomp., THF–hexane). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 1.072 (3H, t, *J* = 7.0 Hz, NOCH<sub>2</sub>Me), 3.731–3.894 (2H, m, NOCH<sub>2</sub>Me), 6.795 (1H, s, OH), 7.488 (1H, s, OH), 7.625 (1H, t, *J* = 7.5 Hz, Ar), 7.751 (1H, d, *J* = 7.2 Hz, Ar), 7.775 (1H, d, *J* = 7.2 Hz, Ar), 7.873 (1H, t, *J* = 7.5 Hz, Ar), 8.650 (1H, s, NH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 13.73 (Me), 71.73 (NOCH<sub>2</sub>), 84.42 (C–OH), 89.14 (C–OH), 123.55 [C(H) Ar], 124.88 [C(H) Ar], 130.54 [C(H) Ar], 132.00 [C<sub>q</sub> Ar], 136.78 [C(H) Ar], 150.72 [C<sub>q</sub> Ar], 155.55 [N(C=O)N], 196.07 (C=O). MS (FAB) *m/z* 265 [M+H]<sup>+</sup> (100), 204 [M+H-H<sub>2</sub>O-HNCO]<sup>+</sup> (95), 177 (31), 161 (21), 150 (27), 131 (30), 105 (33). Anal. Calc. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>: C 54.55, H 4.58, N 10.60. Found: C 54.38, H 4.30, N 10.70.

**B.** Ninhydrin (173 mg, 0.973 mmol) was dissolved in the solution of *N*-ethoxyurea (101 mg, 0.973 mmol) in acetic acid (6 mL) by stirring at 17 °C for 1.5 h, the reaction solution was maintained at 15 °C for 1.5 h, then it was frozen and acetic acid was evaporated under vacuum (3 mmHg). The obtained residue was washed with benzene (6 mL) at 10 °C and dried under vacuum (3 mmHg) giving 254 mg (99 %) mixture of diastereomes of *cis*-3a,8a-dihydroxydiastereomer **9a** (92 %) and *trans*-3a,8a-dihydroxydiastereomer **9b** (8 %). This mixture was extracted by water (12 mL) at 4 °C for 23 h, solid phase was filtered off, dried under vacuum (3mmHg), giving 174 mg (67.6 %) of *cis*-3a,8a-dihydroxydiastereomer **9a**.

#### 1-*n*-Butyloxy-3a*S*,8a*R*-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (**10a**)

**A.** Ninhydrin (183 mg, 1.027 mmol) was dissolved in the solution of *N*-*n*-butyloxyurea<sup>11</sup> (136 mg, 1.027 mmol) in acetic acid (6 mL) by stirring at 18 °C for 3 h. The reaction solution was maintained at 18 °C for 21 h, then it was frozen and acetic acid was evaporated under vacuum (3 mmHg). The obtained residue was washed with water (4 mL) at 5 °C and dried under vacuum (3 mmHg) giving 229 mg (77 %) of *cis*-3a,8a-dihydroxydiastereomer **10a**, colorless crystals, m. p. 163-164 °C (with decomp.). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 0.852 (3H, t, *J* = 7.2 Hz, NO(CH<sub>2</sub>)Me), 1.335 (2H, sex, *J* = 7.2 Hz, NOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Me), 1.464 (2H, quint, *J* = 7.2 Hz, NOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Me), 3.706–3.857 (2H, m, NOCH<sub>2</sub>), 6.750 (1H, s, OH), 7.390 (1H, s, OH), 7.618 (1H, t, *J* = 7.2 Hz, Ar), 7.756 (1H, d, *J* = 6.6 Hz, Ar), 7.777 (1H, d, *J* = 6.6 Hz, Ar), 7.865 (1H, t, *J* = 7.2 Hz, Ar), 8.609 (1H, s, NH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 13.77 (Me), 18.56 (CH<sub>2</sub>), 29.90 (CH<sub>2</sub>), 76.03 (NOCH<sub>2</sub>), 84.37 (C–OH), 89.08 (C–OH), 123.51 [C(H) Ar], 124.86 [C(H) Ar], 130.48 [C(H) Ar], 132.01 [C<sub>q</sub> Ar], 136.71 [C(H) Ar], 150.72 [C<sub>q</sub> Ar], 155.40 [N(C=O)N], 195.96 (C=O). MS (FAB) *m/z* 293 [M+H]<sup>+</sup>(100), 232 [M+H-H<sub>2</sub>O-HNCO]<sup>+</sup> (39), 177 (75), 161(23), 150 (15), 131 (25), 105 (14). Anal. Calc. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>: C 57.53, H 5.52, N 9.58. Found: C 57.36, H 5.71, N 9.37.

**B.** Ninhydrin (138 mg, 0.774 mmol) was dissolved in the solution of *N*-*n*-butyloxyurea<sup>11</sup> (102 mg, 0.774 mmol) in acetic acid (6 mL) at stirring at 19 °C for 1h, the reaction solution was maintained at 17 °C for 2 h, then it frozen and acetic acid was evaporated under vacuum (3 mmHg). The obtained residue was washed by benzene (3 mL), dried under vacuum, giving 209 mg (92%) of *cis*-3a,8a-dihydroxydiastereomer**10a** and *trans*-3a,8a-dihydroxydiastereomer**10b** (94:6). This mixture was extracted by water (5.5 mL) at 4 °C for 26 h, the white precipitate was filtered off, washed with cold water (3.5 mL) and dried under vacuum (3 mmHg) at 20 °C, to give 148 mg (65 %) *cis*-3a,8a-dihydroxydiastereomer **10a**, white powder, m. p. 160-161 °C (with decomp.).

#### 1-Benzoyloxy-3a*S*,8a*R*-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (**11a**)

**A.** Ninhydrin (81.0 mg, 0.459 mmol) was dissolved in the solution of *N*-benzyloxyurea (76.2 mg, 0.459 mmol) in acetic acid (4 mL) by stirring at 16 °C. The reaction solution

was maintained at 16 °C for 25 h, then acetic acid was evaporated under vacuum (3 mmHg). The obtained residue was washed with water (5 mL) at 5 °C and dried under vacuum (3 mmHg), giving 108.4 mg (72 %) *cis*-3a,8a-dihydroxydiastereomer **11a**, colourless crystals, m. p. 174-176 °C (with decomp.). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 4.745 (1H, d, *J* = 10.2 Hz, NOCH<sub>2</sub>), 4.896 (1H, d, *J* = 10.2 Hz, NOCH<sub>2</sub>), 6.850 (1H, s, OH), 7.298–7.386 (3H, m, Ph), 7.396–7.444 (2H, m, Ph), 7.566 (1H, s, OH), 7.634 (1H, t, *J* = 7.5 Hz, C<sub>6</sub>H<sub>4</sub>), 7.749–7.788 (2H, m, C<sub>6</sub>H<sub>4</sub>), 7.884 (1H, t, *J* = 7.5 Hz, C<sub>6</sub>H<sub>4</sub>), 8.719 (1H, s, NH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 78.41 (NOCH<sub>2</sub>), 84.43 (C–OH), 89.17 (C–OH), 123.62 [C(H) C<sub>6</sub>H<sub>4</sub>], 124.84 [C(H) C<sub>6</sub>H<sub>4</sub>], 128.16 [C(H) Ph], 128.33 [C(4)H Ph], 129.01[C(H) Ph], 130.48 [C(H) C<sub>6</sub>H<sub>4</sub>], 131.95 [C<sub>q</sub> C<sub>6</sub>H<sub>4</sub>], 135.48 [C(1) Ph], 136.76 [C(H) C<sub>6</sub>H<sub>4</sub>], 150.72 [C<sub>q</sub> C<sub>6</sub>H<sub>4</sub>], 155.23 [N(C=O)N], 195.89 (C=O). MS (FAB) *m/z* 327 [M+H]<sup>+</sup>(9), 91 Bn<sup>+</sup> (100). Anal. Calc. for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>: C 62.58, H 4.32, N 8.58. Found: C 62.69, H 4.20, N 8.45.

**B.** Ninhydrin (50.1 mg, 0.281 mmol) was dissolved in the solution of *N*-benzyloxyurea (46.7 mg, 0.281 mmol) in acetic acid (3 mL) by stirring at 18 °C for 2 h. The reaction solution was maintained at 16 °C for 14 h, then acetic acid was evaporated under vacuum (3 mmHg). The obtained residue was washed by benzene (4 mL) and dried under vacuum (3 mmHg) to give 86.2 mg (94 %) of mixture of *cis*-3a,8a-dihydroxydiastereomer **11a** and *trans*-3a,8a-dihydroxydiastereomer **11b** (91:9). This mixture was dissolved in THF (2 mL) then hexane (5 mL) was added to it. After the maintaining at 4 °C for 72 h the obtained precipitate was filtered off, dried, extracted by water (3 mL) at 4 °C for 48 h. The resulting precipitate was filtered off and dried under vacuum (3 mmHg), giving 61 mg (66 %) of **11a**.

Crystals of compound **7** were grown from AcOH at 14 °C. The studied crystals are triclinic, C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>5</sub>, at 20 °C, *a* = 7.430(5) Å, *b* = 7.827(4) Å, *c* = 10.237(4) Å, *α* = 76.91(4)°, *β* = 77.88(5)°, *γ* = 66.53(6)°, *V* = 527.0(5) Å<sup>3</sup>, *M<sub>r</sub>* = 236.18, *Z* = 2, space group P1̄, *d<sub>calc.</sub>* = 1.488 g cm<sup>-3</sup>, *μ*(MoK<sub>α</sub>) = 0.122 mm<sup>-1</sup>, *F*(000) = 244.

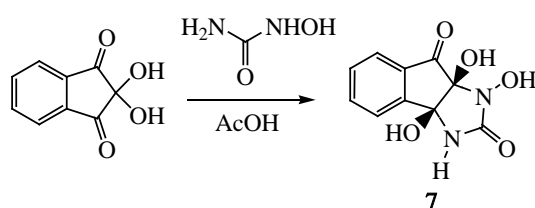
Crystals of compound **10a** were grown from THF-C<sub>6</sub>H<sub>14</sub> at -14 °C. The studied crystals are tetragonal, C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>, at 20 °C, *a* = 22.2342(16) Å, *c* = 6.1638(10) Å, *V* = 3047.1(7) Å<sup>3</sup>, *M<sub>r</sub>* = 292.29, *Z* = 8, space group P4<sub>2</sub>/n, *d<sub>calc.</sub>* = 1.274 g cm<sup>-3</sup>, *μ*(MoK<sub>α</sub>) = 0.098 mm<sup>-1</sup>, *F*(000) = 1232. X-ray structural study of compounds **7** and **10a** was performed on an “Xcalibur 3” diffractometer (MoK<sub>α</sub>-radiation, graphite monochromator, Sapphire-3 CCD detector, ω-scanning, 2θ<sub>max</sub> = 50°).

The structure was solved by the direct methods with the SHELX-2016<sup>12</sup> software. The positions of the hydrogen atoms were located from electron density difference maps and refined by the “riding” model with *U*<sub>iso</sub> = *nU*<sub>eq</sub> of the carrier atoms (*n* = 1.5 for methyl and hydroxyl groups and *n* = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement of the structures against *F*<sup>2</sup> in anisotropic approximation for non-hydrogen atoms was converged to *wR*<sub>2</sub> = 0.194 using 1846 reflections (*R*<sub>1</sub> = 0.078 for 699 reflections with *F* > 4σ(*F*), *S* = 0.903) for compound **7**, *wR*<sub>2</sub> = 0.201 using 2688 reflections (*R*<sub>1</sub> = 0.0695 for 1645 reflections with *F* > 4σ(*F*), *S* = 1.038) for compound **10a**. The

atomic coordinates, molecular geometry parameters, and crystallographic data of compound **7** and **10a** were deposited to the Cambridge Crystallographic Data Center, 12 Union Road, CB2, 1EZ UK [fax:+44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk and is available on request quoting the deposit number CCDC 1976149 (**7**), 1971812 (**10a**).

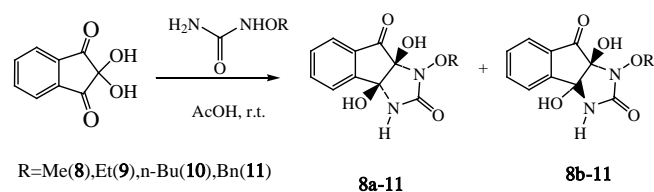
## RESULTS AND DISCUSSION

The ninhydrin interaction with *N*-hydroxyurea in acetic acid at 16–20 °C produces 1,3a,8a-trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione (**7**) as single *cis*-3a(HO),8a(HO)-diastereomer with high yield (Scheme 4). The alternative *trans*-3a(HO),8a(HO)-diastereomer formation was not observed (Scheme 5).



**Scheme 5.** The synthesis of 1,3a,8aR-trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **7**.

Ninhydrin reacts with *N*-alkoxyureas in the same conditions yielding mixtures of diastereomers of 1-alkoxy-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones **8–11** (Scheme 6).



**Scheme 6.** The synthesis of 1-alkoxy-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones **8–11**.

In these mixtures the diastereomers **8a–11a** with *cis* orientation of hydroxyl groups at C-3a, 8a carbon atoms dominate. Usually, the ratio **8a–11a/8b–11b** is 9:1–10:1. The diastereomers **8b–11b** with *trans* orientation of 3a-HO and 8a-HO-groups have been observed in the trace amounts of the reaction mixtures (<sup>1</sup>H NMR). The *cis*-3a,8a-dihydroxy diastereomers **8a–11a** can be easily obtained in pure form by the washing of the reaction mixture with water.

In the <sup>1</sup>H NMR spectra of compounds **7**, **8a–11a** the singlets of protons of *cis* 3a-HO and 8a-HO groups are situated in the different fields (6.64–6.85 ppm and 7.26–7.56 ppm) whereas the singlets of *trans* 3a-HO and 8a-HO moieties of diastereomers **8b–11b** are situated closely in the 6.99–7.17 ppm region (Table 1). The singlets of NH-protons of *cis*-3a,8a-dihydroxy diastereomers **8a–11a** are situated in the lower field than the same singlets of NH-protons of *trans*-3a,8a-dihydroxy diastereomers **8b–11b**.

**Table 1.** The typical <sup>1</sup>H NMR chemical shifts of 3a,8a-HO-protons and NH-protons of compounds **7**, **8a–11a** and **8b–11b**.

<i>cis</i> Diastereomer			<i>trans</i> Diastereomer		
Compd.	shifts, ppm		Compd.	shifts, ppm	
	OH	NH		OH	NH
<b>7</b>	6.646; 7.268	8.409	-	-	-
<b>8a</b>	6.792; 7.524	8.663	<b>8b</b>	7.047	8.534
<b>9a</b>	6.795; 7.488	8.650	<b>9b</b>	6.988;	8.514
<b>10a</b>	6.750; 7.390	8.609	<b>10b</b>	7.000;	8.507
<b>11a</b>	6.850; 7.566	8.719	<b>11b</b>	7.136;	8.595
				7.176	

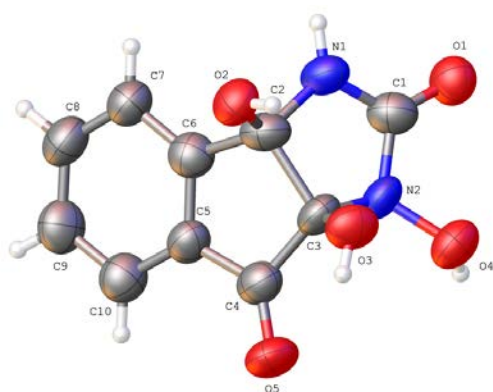
In the <sup>13</sup>C NMR spectra of compounds **7**, **8a–11a** the chemical shifts of carbon atoms connected with HO-groups, NOCH<sub>2</sub> (NOME for compound **8a**) carbon atoms, and the carbon atoms of carbonyl groups are typical (Table 2).

**Table 2.** The typical <sup>13</sup>C NMR chemical shifts of carbon atoms of compounds **7**, **8a–11a**.

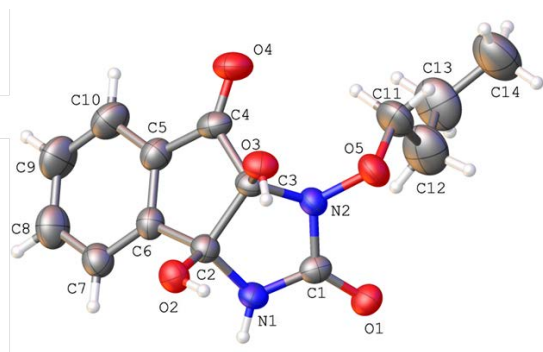
Compound	Shifts, ppm			
	C–OH	NOCH <sub>2</sub>	NC(=O)N	C=O
<b>7</b>	84.33; 89.36		156.05	195.63
<b>8a</b>	84.37; 88.92	64.36	155.19	196.14
<b>9a</b>	84.42; 89.14	71.73	155.55	196.07
<b>10a</b>	84.37; 89.08	76.03	155.40	195.96
<b>11a</b>	84.43; 89.17	78.41	155.23	195.89

Finally, the structure of compound **7** and **10a** have been proved by XRD study (Figures 1–3, Tables 3 and 4). The molecular structure of compound **7** is similar to the molecular structure of compound **10a**. The molecular structures of compounds **7** and **10a** contains *cis*-fused indane and imidazolidine moiety (Fig. 1, 2) with the angle between the indane and imidazolidine planes is 64° (**7**), 60° (**10a**). At that two hydroxyl groups are *cis*-oriented to each other (the O(2)–C(2)–C(3)–O(3) torsion angle in Table 3). However, some difference is revealed in the compensation of steric repulsion appeared due to *cis*-fusing. The C(3) atom deviates on 0.42 Å from the mean plain of remaining atoms of the heterocycle and on 0.24 Å from the mean plane of five-membered carbocycle in molecule **7**. In molecule **10a**, the N(2) atom deviates on 0.20 Å from the mean plain of remaining heterocyclic atoms while the carbocycle is planar. The endocyclic C(2)–C(3) bond which is joint for *cis*-fused cycles is elongated (Table 3) as compared to C(sp<sup>3</sup>)–C(sp<sup>3</sup>) ordinary bond (1.54 Å)<sup>13</sup> that is typical.<sup>14,15</sup>





**Figure 1.** Molecular structure of 1,3a*S*,8a*R*-trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **7** with atoms represented by thermal vibration ellipsoids at 50 % probability level.



**Figure 2.** Molecular structure of 1-*n*-butyloxy-3a*S*,8a*R*-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **10a** with atoms represented by thermal vibration ellipsoids at 50 % probability level.

**Table 3.** Some molecular characteristics in the **7** and **10a** crystals.

Bond	<b>7</b>	<b>10a</b>
O(2)–C(2)–C(3)–O(3), °	-21.8(7)	6.3(3)
C(2)–C(3), Å	1.619(7)	1.585(3)
C(3)–C(4), Å	1.575(8)	1.535(3)
C(2)–C(6), Å	1.557(8)	1.499(3)
O(2)–C(2), Å	1.439(6)	1.395(2)
O(3)–C(3), Å	1.411(6)	1.390(2)
N(1)–C(1), Å	1.369(7)	1.334(2)
N(2)–C(1), Å	1.409(7)	1.364(2)
C(4)=O(4), Å	1.206(3)	
C(1)=O(1), Å	1.242(2)	1.272 (6)
C(4)=O(5), Å		1.250(7)
∑N(1), °	360	360
∑N(2), °	341.9	348.5

The C(3)–C(4) bond in molecules **7**, **10a** is elongated (Table 3) compare to average length of C(sp<sup>3</sup>)–C(sp<sup>2</sup>) ordinary bond (1.510 Å).<sup>13</sup> In the molecule **7**, the endocyclic C(2)–C(6) bond is elongated compare to the same C(2)–C(6) bond in the molecule **10a** (Table 3) and average length of C(sp<sup>3</sup>)–C(sp<sup>2</sup>) ordinary bond.

The O(2)–C(2) and O(3)–C(3) ordinary bonds are similar in molecules **7** and **10a** (Table 3). In molecules **4a**, **5**, **6** the similar *cis* oriented vicinal (H)O–C bonds are so different.<sup>9,10</sup>

The N(1) atom has a planar configuration while the N(2) atom has a pyramidal configuration (Table 3) in the both molecules. At that the N(1)–C(1) amide bond is shorter than N(2)–C(1) amide bond (Table 3) indicating stronger conjugation between N(1) lone pair and C(1)=O(1) carbonyl bond as compared to conjugation between N(2) lone pair and C(1)=O(1) carbonyl bond in both molecules. The similar phenomenon is typical for 3-hydroxy- and 3-alkoxy-5-arylimidazolidine-2,4-diones,<sup>6,8</sup> *N*-methoxyurea<sup>11</sup> and in the cyclic *N*-alkoxyureas **5,6**.<sup>10</sup>

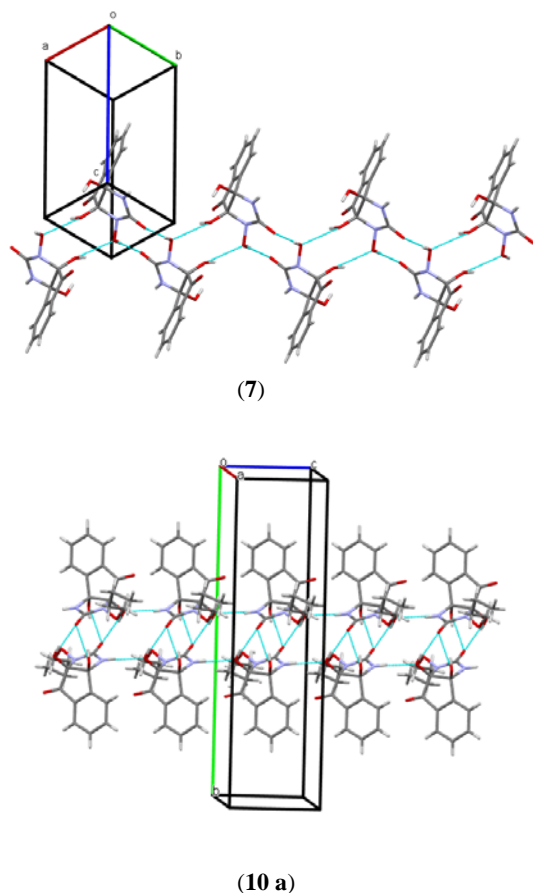
The N(2)–O(4)H bond [1.429(5) Å] in molecule **7** is longer than N(2)–O(5)Bu bond [1.397(2) Å] in molecule **10a**, and N–OH bond [1.398(7) Å] in molecule **4a**,<sup>9</sup> N–OH bond [1.3745(17) Å] in 3-hydroxy-5-phenylimidazolidine-2,4-dione.<sup>6</sup>

In molecule **10a** the butyloxy moiety has +*ac*-conformation to the C(1)–N(2) endocyclic bond [the C(1)–N(2)–O(5)–C(11) torsion angle is 115.1(2)°] and the butyl fragment is turned relatively to the N(2)–O(5) bond [the N(2)–O(5)–C(11)–C(12) torsion angle is -75.6(2)°]. The C(13) and C(14) atoms are disordered on two position **A** and **B** with the population ratio of 60:40 due to the rotation around the C(11)–C(12) bond. The O(5)–C(11)–C(12)–C(13) torsion angle is -175.7(2)° in conformer **A** and 167.7(2)° in conformer **B** while the C(11)–C(12)–C(13)–C(14) torsion angle is -168.3(2)° in conformer **A** and 68.7(2)° in conformer **B**. In the both molecules **7** and **10a** the ketone carbonyl bond is shorter as compared to urea carbonyl bond.

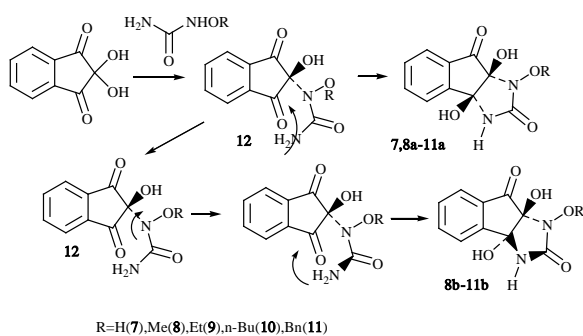
In the crystal phase, molecules **7** and **10a** form the centrosymmetrical dimers bound by the O(4)–H(4)...O(1) (**7**), O(2)–H(2)...O(1) and O(3)–H(3)...O(1) (**10a**) intermolecular hydrogen bonds (Table 3, Figure 3). These dimers form the chains along [1 0 0] crystallographic direction due to the intermolecular hydrogen bond N(1)–H(1)...O(5) in the **7** crystal and along [001] crystallographic direction due to the N(1)–H(1)...O(3) intermolecular hydrogen bond in the **10a** crystal (Table 3, Figure 3). The neighboring chains link by the O(3)–H(3)...O(4) and O(2)–H(2)...O(1) intermolecular hydrogen bonds in the **10a** crystal (Table 4).

**Table 4.** Intermolecular hydrogen bonds in the **7** and **10a** crystals.

Crystal	Hydrogen bond	Symmetry operations	H...A, Å	D–H...A, deg.
<b>7</b>	O(4)–H(4)...	1-x, 2-y,	1.94	160
	H(4)...O(1)	2-z		
	N(1)–H(1)...	-1+x, y,	2.21	156
	H(1)...O(5)	z		
	O(3)–H(3)...	2-x, 1-y,	2.20	139
	H(3)...O(4)	2-z		
	O(2)–H(2)...	1-x, 1-y,	2.11	161
	H(2)...O(1)	2-z		
	O(2)–H(2)...	1-x, 1-y,	2.01	156
	H(2)...O(1)	1-z		
<b>10a</b>	O(3)–H(3)...	1-x, 1-y,	1.92	165
	H(3)...O(1)	1-z		
	N(1)–H(1)...	x, y,	2.07	173
	H(1)...O(3)	-1+z		



**Figure 3.** The arrangement of the molecules in compound **7**, **10a** in the crystal.



**Scheme 7.** The proposed formation mechanism of the compounds **7–11**.

The formation of tricyclic compounds **7–11** may be realized in the following way (Scheme 7). At the first stage the ninhydrin's interaction with *N*-hydroxyurea or *N*-alkoxyureas on *N*-hydroxyamino group or *N*-alkoxyamino group takes place, forming ureas **12**. In the same manner the arylglyoxals react with *N*-hydroxyurea,<sup>6–8</sup> *N*-alkoxyureas,<sup>9</sup> *N*-alkoxy-*N'*-arylureas<sup>10</sup> and *N*-alkoxy-*N'*-alkylureas.<sup>10</sup>

On the second stage compounds **7** and **8a–11a** are formed due to the intramolecular cyclization. In these heterocycles the vicinal HO-groups of hemiaminal moieties have *cis* mutual orientation.

In the ureas **12** the rotation around N–C bond with further cyclization gives diastereomers **8b–11b** having *trans* mutual orientation of the vicinal HO-groups. Probably, this rotation is retarded and proceeds more slowly than the cyclization yielding *cis*-3a,8a-dihydroxydiastereomers **7** and **8a–11a**.

## CONCLUSIONS

We have found that ninhydrin reacts with *N*-hydroxyurea and *N*-alkoxyureas in acetic acid with the predominant formation of the diastereomers of the 1,3a,8a-trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione and 1-alkoxy-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones having the *cis*-orientation of 3a,8a-HO-groups. The structures of 1,3a,8aR-trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **7** and 1-*n*-butyloxy-3a,8aR-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **10a** have been investigated by XRD study.

## REFERENCES

- Shapiro, R., Chatterjee, N., Cyclization Reactions of Ninhydrin with Aromatic Amines and Ureas, *J. Org. Chem.*, **1970**, 35(2), 447–450. <https://doi.org/10.1021/jo00827a034>
- Van Slyke, D. D., Hamilton, P. B., The Synthesis and Properties of Ninhydrin Ureide. *J. Biol. Chem.*, **1943**, 150(2), 471–476.
- Azizian, J., Karimi, A. R., Soleimani, E., Mohammadi, A.A., Mohammadzadeh, M. R., Highly Functionalized Dihydrofuran Derivatives: Synthesis by Diastereoselective Intramolecular Wittig Reaction, *Heteroatom. Chem.*, **2006**, 17(4), 277–279. DOI: 10/1002hc
- Jong, J. A. W., Moret, M.-E., Verhaar, M. C., Hennink, W. E., Gerritsen, K. G. F., Van Nostrum, C. F., Effect of Substituents on the Reactivity of Ninhydrin with Urea, *ChemistrySelect*, **2018**, 3, 1224–1229. DOI: 10/1002slct201800040.
- Jong, J. A. W., Smakman, R., Moret, M.-E., Verhaar, M. C., Hennink, W. E., Gerritsen, K. G. F., Van Nostrum, C. F., Reactivity of (Vicinal) Carbonyl Compounds with Urea, *ACS Omega*, **2019**, 4, 11928–11937. DOI: 10/10021acsomega.9b01177
- Shtamburg, V. G., Anishchenko, A. A., Shtamburg, V. V., Shishkin, O. V., Zubatyuk, R. I., Mazepa, A. V., Rakipov, I. M., Kostyanovsky, R. G., Synthesis and crystal structure of new imidazolidine-2,4-dione and imidazolidin-2-one derivatives, *Mendeleev Commun.*, **2008**, 18, 102–104. DOI: 10.1016/j.mencom.2008.03.018.
- Kostyanovsky, R. G., Shtamburg, V. G., Shishkin, O. V., Zubatyuk R. I., Shtamburg, V. V., Anishchenko, A. A., Mazepa, A. V., Pyramidal nitrogen in the crystal of *N*-[(benzoyl)-(hydroxy)methyl]-*N*-benzyloxy-*N'*-(2-bromophenyl)urea. *Mendeleev Commun.*, **2010**, 20, 167–169. DOI: 10.1016/j.mencom.2010.05.015.
- Shtamburg, V. G., Shtamburg, V. V., Anishchenko, A. A., Zubatyuk R. I., Mazepa, A. V., Klotz, E. A., Kravchenko, S. V., Kostyanovsky, R. G., Single-stage synthesis of 3-hydroxy- and 3-alkoxy-5-arylimidazolidine-2,4-diones by reaction of arylglyoxal hydrates with *N*-hydroxy- and *N*-alkoxyureas, *Chem. Heterocycl. Comp.*, **2015**, 51(6), 553–559, DOI 10.1007/s10593-015-1735-0
- Shtamburg, V. G., Shtamburg, V. V., Anishchenko, A. A., Mazepa, Shishkina, S. V., Konovalova, I. S., Synthesis and structure of 3,4,5-trihydroxy-5-(4-nitrophenyl)imidazolidin-2-one, *Eur. Chem. Bull.*, **2019**, 8(4), 110–114. DOI: 10.17628/ecb.2019.8.110-114.

- <sup>10</sup>Shtamburg, V. G., Shtamburg, V. V., Anishchenko, A. A., Shishkina, S. V., Mazepa, A. V., Konovalova, I. S., 3-Alkoxy-1,5-diaryl-4,5-dihydroxyimidazolidin-2-ones and 3-Alkoxy-1-alkyl-5-aryl-4,5-dihydroxyimidazolidin-2-ones: Synthesis and Structure, *Eur. Chem. Bull.*, **2019**, 8(9), 282–290. DOI: <http://dx.doi.org/10.17628/ecb.2019.8.282-290>
- <sup>11</sup>Shtamburg, V. G., Klots, E. A., Pleshkova, A. P., Avramenko, V. I., Ivonin, S. P., Tsygankov, A. V., Kostyanovsky, R. G., Geminal systems. 50. Synthesis and alcoholysis on *N*-acyloxy-*N*-alkoxy derivatives of ureas, carbamates and benzamide, *Russ. Chem. Bull., Int. Ed.*, **2003**, 52(10), 2251–2260. <https://doi.org/10.1023/B:RUCB.0000011887.405.29.b0>
- <sup>12</sup>Sheldrick, G. M., SHELXT – integrated space-group and crystal-structure determination, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, **2015**, A71(1), 3–8. <https://doi.org/10.1007/S2053273314026370>
- <sup>13</sup>Burgi, H.-B., Dunitz, J. D., *Structure correlation*. Vol. 2. VCH. Weinheim, 1994, 741–784. <https://doi.org/10.1107/S0108768195009931>
- <sup>14</sup>Agapiou, K., Cauble, D. F., Krische, M. J., Copper-Catalyzed Tandem Conjugate Addition–Electrophilic Trapping: Ketones, Esters, and Nitriles as Terminal Electrophiles, *J. Am. Chem. Soc.*, **2004**, 126(14), 4528–4529. DOI: 10.1021/ja030603l.
- <sup>15</sup>Deng, Q.-H., Wadepohl, H., Gade, L. H., Highly Enantioselective Copper-Catalyzed Alkylation of  $\beta$ -Ketoesters and Subsequent Cyclization to Spirolactones/Bi-spirolactones, *J. Am. Chem. Soc.*, **2012**, 134(6), 2946–2949. DOI: 10.1021/ja211859w.

Received: 19.01.2020.

Accepted: 19.04.2020.