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

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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 cis-orientation of 3a,8a-HO-groups. The X-ray structural analysis of 1,3aS,8aR-trihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione and 1-n-butyloxy-3a,8aR-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione has demonstrated their specific structural features.

INTRODUCTION

Nitrogen-containing heterocyclic systems, such as hydantoins 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,1,4 ninhydrin (indane-1,2,3-dione) 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.](image)

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 and pharmaceuticals.3,5

The study of the vicinal polycarbonyl compounds interaction with N-hydroxyurea and its derivatives4,9 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.6–10

Earlier we have found8 that most of arylglyoxals reacted with N-hydroxyurea and N-alkoxyureas in acetic acid producing 3-hydroxyhydantoins 2 and 3-alkoxyhydantoins 3 (Scheme 2).

![Scheme 2: Interaction of the most of arylglyoxals with N-hydroxyurea and N-alkoxyureas in the acetic acid.](image)

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.6 4-Nitrophenylglyoxal, however, reacts with N-hydroxyurea producing9 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.](image)

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

Moreover, 4-nitrophenylglyoxal diastereoselectively reacts with N-alkoxy-N’-arylureas and N-alkoxy-N’-alkyureas in acetic acid at 17–20°C mainly producing 3-alkoxy-1-aryl-4,5,5S-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones 5 and 3-alkoxy-1-alkyl-4,5S-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones 6.10 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'-arylureas.

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

1HNMR spectra were recorded on a Varian VXP-300 spectrometer (300 MHz). 13C NMR spectra were recorded on a Varian VXP-300 spectrometer (75 MHz). The solvent DMSO-d6 was used. 1HNMR chemical shifts relative to the residual solvent protons as an internal standard [(CD3)2SO: 39.52 ppm]. Mass spectra were recorded on a VG 70-70EQ mass spectrometer in fast atom bombardment mode (FAB). The 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 ºC. The reaction solution was maintained at 8 ºC for 23 h, then it was heated to 16 ºC, the obtained white precipitate was filtered out, dried under vacuum (3 mmHg) giving 190 mg (98 %) cis-3a,8a-dihydroxydiasteromer of 7, colorless crystals, m. p. 169–171 ºC (with decomp.). This mixture was extracted by water (10 mL) at 4 ºC, the obtained precipitate was filtered off, dried under vacuum (3 mmHg) giving 142 mg (67 %) of cis-3a,8a-dihydroxydiasteromer of 8a, colorless crystals, m. p. 197-199 ºC (with decomp., THF–hexane).

1H NMR (300 MHz, DMSO-d6) δ = 3.598 (3H, s, NOE), 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). 

B. Ninhydrin (150.3 mg, 0.844 mmol) was dissolved in acetic acid (6 mL) by stirring at 20 ºC for 1h. The reaction solution was maintained at 20 ºC for 1h, maintained at 5ºC for 20 h, then acetic acid was evaporated under vacuum (3 mmHg) at 18 ºC, the residue was extracted with water (3 mL) at 5ºC. The obtained precipitate was filtered off, dried under vacuum (3 mmHg) giving 142 mg (67 %) of cis-3a,8a-dihydroxydiasteromer of 8a, colorless crystals, m. p. 169-171 ºC (with decomp.).

1-Methoxy-3aS,8aR-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 ºC for 1h. The reaction solution was maintained at 20 ºC for 1h, maintained at 5ºC for 20 h, then acetic acid was evaporated under vacuum (3 mmHg) at 18 ºC, the residue was extracted with water (3 mL) at 5ºC. The obtained precipitate was filtered off, dried under vacuum (3 mmHg) giving 142 mg (67 %) of cis-3a,8a-dihydroxydiasteromer of 8a, colorless crystals, m. p. 197-199 ºC (with decomp., THF–hexane).

1H NMR (300 MHz, DMSO-d6) δ = 3.598 (3H, s, NOE), 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). 13C NMR (75 MHz, DMSO-d6): δ = 64.36 (NOMe), 84.37 (C=O), 88.92 (C=O), 123.63 (C(H) Ar), 124.90 (C(H) Ar), 130.57 (C=O) Ar), 131.91 (C=O), 131.83 (C=O Ar), 150.73 (C=O Ar), 155.19 [N(C=O)N], 196.14 (C=O). MS (FAB) m/z 501(2M+H)+ (10), 251 (M+H)+ (100), 191 (30), 161 (16).

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 ºC for 1 h. The reaction mixture was maintained at 16 ºC for 2 h, then acetic acid was evaporated under vacuum (3 mmHg) at 20 ºC, giving 182 mg (99 %) of mixture of cis-3a,8a-dihydroxydiasteromer 8a (89 %) and trans-3a,8a-dihydroxydiasteromer 8b (11 %). This mixture was extracted by water (10 mL) at 4ºC 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 ºC, giving 91 mg (50 %) of 8a.

1-Ethoxy-3aS,8aR-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 ºC for 6 h, the reaction solution was maintained at 17 ºC 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 ºC, dried under vacuum (3 mmHg), giving 239 mg (72 %) of cis-3a,8a-dihydroxydiasteromer of 9a, colorless crystals, m. p. 161-163 ºC (with decomp., THF–hexane).

1H NMR (300 MHz, DMSO-d6): δ = 1.072 (3H, t, J = 7.0 Hz, NOCH3Me), 3.731–3.894 (2H, m, NOCH3Me), 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). 

13C NMR (75 MHz, DMSO-d6): δ = 13.73 (Me), 71.73 (NOCH3), 84.42 (C=O), 89.14 (C=O), 123.55 (C(H) Ar), 124.88 (C(H) Ar), 130.54 (C=O) Ar), 132.00 (C=O Ar), 136.78 (C(H) Ar), 150.72 (C=O Ar), 155.55 [N(C=O)N], 196.07 (C=O). MS (FAB) m/z 265 [M+H]+(100), 204 [M+H-H2O-HNO2]+(95), 177 (31), 161 (21), 150 (27), 131 (30), 105 (33).

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**Reaction of ninhydrine with N-hydroxy- and N-alkoxyureas**

**Section A-Research paper**

**A.** Ninhydrin (183 mg, 1.027 mmol) was dissolved in the solution of N-benzoxyleurea(1) (136 mg, 1.027 mmol) in acetic acid (6 mL) by stirring at 18 °C for 3 h. The reaction solution was washed with benzene (4 mL) at 4 °C for 23 h, solid phase was filtered off, dried under vacuum (3 mmHg), giving 174 mg (67.6 %) of cis-3a,8a-dihydroxydiaoxydisteraeme 9a.

**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-dihydroxydiaoxydisteraeme 9a (92 %) and trans-3a,8a-dihydroxydiaoxydisteraeme 9b (8 %). This mixture was extracted by water (12 mL) at 4 °C for 23 h, solid phase was filtered off, dried under vacuum (3 mmHg), giving 174 mg (67.6 %) of cis-3a,8a-dihydroxydiaoxydisteraeme 9a.

**1-n-Butyloxy-3a,8aR-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-benzoxyleurea(1) (136 mg, 1.027 mmol) in acetic acid (6 mL) by stirring at 18 °C for 3 h. The reaction solution was washed with benzene (4 mL) at 4 °C for 23 h, solid phase was filtered off, dried under vacuum (3 mmHg), giving 174 mg (67.6 %) of cis-3a,8a-dihydroxydiaoxydisteraeme 10a, colorless crystals, m. p. 163-164 °C (with decomp.). 1H NMR (300 MHz, DMSO-d6): δ = 4.754 (1H, d, J = 10.2 Hz, NOCH3), 4.896 (1H, d, J = 10.2 Hz, NOCH3), 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, C6H4), 7.749–7.788 (2H, m, C6H4), 7.884 (1H, t, J = 7.5 Hz, C6H4), 8.719 (1H, s, NH). 13C NMR (75 MHz, DMSO-d6): δ = 78.41 (NOCH3), 84.43 (C=O), 89.17 (C=O), 123.62 [C(H) C6H4], 124.84 [C(H) C6H4], 128.16 [C(H) Ph], 128.33 [C(4)H Ph], 129.01 [C(8)H Ph], 130.48 [C(H) C6H4], 131.95 [C9(C6H4)], 135.48 [C(1) Ph], 136.76 [C(H) C6H4], 150.72 [C9(C6H4)], 155.23 [N(C=O)N], 195.89 (C=O), MS (FAB) m/z 327 [M+H]+, 91 (M+, 9.8 %). Anal. Calc. for C17H14N2O5: C 62.69, H 4.20, N 8.45. 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-benzyloxyleurea (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-dihydroxydiaoxydisteraeme 11a and trans-3a,8a-dihydroxydiaoxydisteraeme 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.

**Section B-Experimental**

**A.** Ninhydrin (183 mg, 1.027 mmol) was dissolved in the solution of N-benzoxyleurea(1) (136 mg, 1.027 mmol) in acetic acid (6 mL) by stirring at 18 °C for 3 h. The reaction solution was washed with benzene (4 mL) at 4 °C for 23 h, solid phase was filtered off, dried under vacuum (3 mmHg), giving 174 mg (67.6 %) of cis-3a,8a-dihydroxydiaoxydisteraeme 9a.

**1-Benzyloxy-3a,8aR-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-benzyloxyleurea (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 refi ned by the “riding” model with U iso = nU eq of the atoms were located from electron density difference maps and refined by the “riding” model with U iso = nU eq of the hydrogens approximated for non- hydrogen atoms was converged to wR2 = 0.194 using 1846 reflections (R1 = 0.078 for 699 reflections with F>4σ(F), S = 1.038). Full-matrix least- squares refinement of the structures against F 2 in anisotropic approximation for non- hydrogen atoms was converged to wR2= 0.194 using 1846 reflections (R1 = 0.078 for 699 reflections with F>4σ(F), S = 1.038). This mixture was washed with benzene (4 mL) and dried under vacuum (3 mmHg) to give 86.2 mg (94 %) of mixture of cis-3a,8a-dihydroxydiaoxydisteraeme 11a and trans-3a,8a-dihydroxydiaoxydisteraeme 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, C10H8N2O5, 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 = 5270(5) Å3, Mw = 236.18, Z = 2, space group P1, dcalc = 1.488 g cm⁻³, µ(MoKα) = 0.122 mm⁻¹, F(000) = 244.

**Crystals of compound 10a were grown from THF-CdH14 at -14°C.** The studied crystals are tetragonal, C14H16N2O5, at 20 °C, a = 22.2342(16) Å, c = 6.1638(10) Å, V = 3047.1(7) Å³, Mw = 292.29, Z = 8, space group P42/n, dcalc = 1.274 g cm⁻³, µ(MoKα) = 0.098 mm⁻¹, F(000) = 1232. X-ray structural study of compounds 7 and 10a was performed on an “Xcalibur 3” diffractometer (MoKα-radiation, graphite monochromator, Sapphire-3 CCD detector, ω-scanning, 20 range 50°).

**The structure was solved by the direct methods with the SHIELDX-2016 software.** The positions of the hydrogen atoms were located from electron density difference maps and refined by the “riding” model with Uiso = Ueq 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 F² in anisotropic approximation for non-hydrogen atoms was converged to wR2= 0.194 using 1846 reflections (R1 = 0.078 for 699 reflections with F>4σ(F), S = 0.903) for compound 7, wR2 = 0.201 using 2688 reflections (R1 = 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 requesting 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 1,3aS,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 (1H 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 1H NMR spectra of compounds 7, 8a–11a the chemical shifts of carbon atoms connected with HO-groups, NOCH2 (NOMe for compound 8a) carbon atoms, and the carbon atoms of carbonyl groups are typical (Table 2).

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 plane 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 plane 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(sp3)–C(sp3) ordinary bond (1.54 Å) that is typical.14,15
The C(3)-C(4) bond in molecules 7, 10a is elongated (Table 3) compare to average length of C(sp^3)-C(sp^3) ordinary bond (1.510 Å).13 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^3)-C(sp^3) ordinary bond.

The C(3)-C(4) bond in molecules 7, 10a is elongated (Table 3) compared to average length of C(sp^3)-C(sp^3) ordinary bond (1.510 Å).13 In the molecule 7, the endocyclic C(2)-C(6) bond is elongated compared to the same C(2)-C(6) bond in the molecule 10a (Table 3) and average length of C(sp^3)-C(sp^3) 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.9,10

The N(1) atom has a planar configuration while the N(2) atom has a pyramidal configuration (Table 3) in 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,6,8 N-methoxyurea11 and in the cyclic N-alkoxyureas 5,6,10

The N(2)-O(4) bond [1.429(5) Å] in molecule 7 is longer than N(2)-O(5) bond [1.397(2) Å] in molecule 10a, and N- OH bond [1.398(7) Å] in molecule 5,6,10 N-OH bond [1.374(17) Å] in 3-hydroxy-5-phenylimidazolidine-2,4-dione.6

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 [0 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).

| Crystal Hydrogen bond | Symmetry operations | H...A, Å | D-H...A, deg. |
|-----------------------|---------------------|----------|--------------|
| O(4)-H(4)...O(1)      | 1-x, 2-y, z         | 1.94     | 160          |
| N(1)-H(1)...O(5)      | 2-z                 | 2.21     | 156          |
| O(3)-H(3)...O(4)      | 2-x, 1-y, 2-z       | 2.20     | 139          |
| O(2)-H(2)...O(1)      | 1-x, 1-y, 2-z       | 2.11     | 161          |
| O(2)-H(2)...O(1)      | 1-x, 1-y, 2-z       | 2.01     | 156          |
| O(3)-H(3)...O(4)      | 1-z                 | 1.92     | 165          |
| O(1)-H(1)...O(3)      | 2-z                 | 2.07     | 173          |

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

| Bond     | 7          | 10a         |
|----------|------------|-------------|
| 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     | 1.141(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       |
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-(3a,8a-dihydroxy-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-dione 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-butoxy-3aS,8aR-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione 10a have been investigated by XRD study.

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