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


Keywords: 4-Nitrophenylglyoxal, N-alkoxy-N’-aryleureas, N-alkoxy-N’-alkylureas, 3-alkoxy-1,5-diaryl-4,5-dihydroxyimidazolidin-2-ones, 3-alkoxy-1-alkyl-5-aryl-4,5-dihydroxyimidazolidin-2-ones, synthesis, structure.

It has been found that 4-nitrophenylglyoxal reacts with N-alkoxy-N’-aryleureas and N-alkoxy-N’-alkylureas in acetic acid medium with the selective formation of the diastereomers of the 3-alkoxy-1,5-diaryl-4,5-dihydroxyimidazolidin-2-ones and 3-alkoxy-1-alkyl-5-aryl-4,5-dihydroxyimidazolidin-2-ones with cis-orientation of OH-groups. The X-ray structural analysis of 3-propoxy-4S,5S-4,5-dihydroxy-1-(4-methylphenyl)-5-(4-nitrophenyl)imidazolidin-2-one has demonstrated this structural feature of these compounds.

INTRODUCTION

Arylglyoxals are widely used in syntheses of heterocycles as syntones.1-6 But the study of the arylglyoxals interaction with N-hydroxyurea7-9 and its derivatives8,10 has started recently and needs to be continued.

Arylglyoxals such as phenyl-, 4-bromophenyl-, 4-chlorophenyl-, 4-fluorophenyl-, 4-methoxyphenyl- and 4-methylglyoxal easily react with N-hydroxyurea in acetic acid medium (Scheme 1) at the room temperature yielding the proper 5-aryl-3-hydroxyimidazolidine-2,4-diones (5-aryl-3-hydroxyhydantoins) 1a-f.8 However, 4-nitrophenylglyoxal in acetic acid medium at room temperature reacts with N-hydroxyurea giving only a mixture of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones, 2a and 3a, in molar ratio near 3:1 (room temp., 25 h).9 3-Hydroxy-5-(4-nitrophenyl)hydantoin (1g) is not formed. This example has demonstrated, that the presence of a strong electron-withdrawing substituent on the benzene ring of arylglyoxals prevents a further conversion of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones into 5-aryl-3-hydroxyimidazolidin-2,4-diones.9

We have obtained similar results in aqueous medium. 4-Nitrophenylglyoxal8 and 4-chlorophenylglyoxal7 form only the mixtures of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones (2a,b and 3a,b) at 14-20 °C (Scheme 2).

![Scheme 1. Arylglyoxal’s interaction with N-hydroxyurea in acetic acid (Ref. 8).](image)

Scheme 2. Interaction of 4-nitrophenylglyoxal hydrate and 4-chlorophenylglyoxal hydrate with N-hydroxyurea in aqueous medium.

In these mixtures, the diastereomers of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones (2a, 2b) with cis orientation of hydroxyl groups at C-4,5 carbon atoms are the main products.7,9 The structure of compounds 2a,b has been proved by XRD study.7,9

Phenylglyoxal reacts with N-hydroxyurea in aqueous solution at the room temperature, forming the mixture of unstable 3,4,5-trihydroxy-5-phenylimidazolidin-2-ones (2c,3c) and 3-hydroxy-5-phenylhydantoin (1a).7,8 The compounds 2c and 3c are easily transformed to hydantoin 1a by heating.7,8

4-Methoxyphenylglyoxal and 4-methylphenylglyoxal form with N-hydroxyurea a mixture of 5-aryl-3-hydroxyhydantoins (1c,1d) and acyclic ureas (4c,4d)7 (Scheme 3).
Substituted 3-alkoxy-4,5-dihydroxyimidazolin-2-ones

Section A-Research paper

But the reaction between phenylglyoxal and N-benzylxy-N'-2-bromophenyl)urea (6d) and N-ethoxy-N'-2-bromophenyl)urea (6d) in dichloromethane solution (Scheme 6) at room temperature gives only acyclic ureas (10a,b). It is probable that the bulky ortho-bromo substituent prevents the further cyclization. The structure of ureas 10a,b has been confirmed by XRD study. In the crystalline state, compound 10a exists in two forms (10aA and 10aB), which are distinguished by the pyramidal degree of the acyclic amide nitrogen atom. The sum of bond angles centered of this atom (Σβ) is 336.0(3)° and 341.2(3)° in the molecules 10aA and 10aB, respectively. The urea 10b exists in the single form, the sum of bond angles centered on the nitrogen atom is 340.0(3)°.

So, the goal of our current research was to investigate the interaction of 4-nitrophenylglyoxal with N-alkoxy-N'-arylyreas 6 in acetic acid medium.

EXPERIMENTAL

1H NMR spectra were recorded on a Varian VXP-300 spectrometer and Varian Jemiini 400 spectrometer (300 and 400 MHz, respectively). 13C NMR spectra were recorded on a Varian VXP-300 spectrometer (75 MHz) and Varian Jemiini 400 spectrometer (100 MHz). The solvents were DMSO-d6 (for the compounds 6a, 11a,g, 13b and 14a, b) and CDCl3 (for the compounds 6a, 13a and 14a). 1H NMR chemical shifts were reported relative to the residual solvent protons as an internal standard ((CD3)2SO: 2.500 ppm) or with TMS as an internal standard (in CDCl3). Solvent carbon atoms served as an internal standard for 13C NMR spectra ((CD3)2SO: 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. 4-Nitrophenylglyoxal hydrate was obtained according to published procedures.

N-Ethoxy-N'-phenylurea (6a)

This compound was obtained according to published procedures, yield was 60 %, colorless crystals, m.p. 101-104 °C. 1H NMR (400 MHz, DMSO-d6): δ = 1.213 (3H, t, J = 7.2 Hz, CH3), 3.823 (2H, CH2OH), 7.257 (2H, t, J = 7.7 Hz, C(4)H Ph), 7.567 (2H, t, J = 7.6 Hz, C(2)H Ph), 7.708 (1H, s, NHO). MS (FAB) m/z 336.0(3)° and 341.2(3)°. The urea 10b exists in the single form, the sum of bond angles centered on the nitrogen atom is 340.0(3)°.

N-Methoxy-N'-phenylurea (6e)

A solution of phenyl isocyanate (918 mg, 7.706 mmol) in dry benzene (8 mL) was added to the solution of methoxyamine (444 mg, 9.434 mmol) in dry benzene (4
N-Benzoyloxy-N'-(benzyloxy)urea (6f)

This compound was obtained as colourless crystals, yield 92 %, m.p. 109-110 °C. 1H NMR (400 MHz, CDCl3): δ = 8.26 (2H, t, J = 7.2 Hz, C(4)H Ph), 8.21 (2H, d, J = 8.8 Hz, C(2)H, C(6)H C6H4Br), 8.40 (1H, t, J = 7.6 Hz, NOCH2), 7.98 (1H, s, NHO), 7.94 (1H, s, NHO). MS (FAB) m/z 329 [M+H]+ (100), 289 [M+H]+(95), 287 [M+H]+ (100), 158 (35), 156 (75), 137 (100), 121 (67). Anal. Calc. for C20H17BrN2O2: C 58.61, H 5.93, N 16.86. Found: C 58.73, H 5.89, N 16.29.

N-Butyloxy-N'-(4-bromophenyl)urea (6j)

Obtained as colourless crystals, yield 61 %, m.p. 104-105 °C. 1H NMR (400 MHz, DMSO-d6): δ = 6.98 (3H, s, NOME), 6.984 (1H, t, J = 7.6 Hz, C(4)H Br), 7.255 (2H, t, J = 7.6 Hz, C(3)H, C(5)H Ph), 7.575 (2H, d, J = 7.8 Hz, C(2)H, C(6)H Ph), 8.840 (1H, s, NH), 9.482 (1H, s, NHO). MS (FAB) m/z 333 [2M+H]+ (95), 289 [M+H]+ (95), 287 [M+H]+ (100), 273 (17), 271 (17), 209 (40). Anal. Calc. for C17H16BrN2O2: C 46.01, H 5.26, N 9.76. Found: C 46.13, H 5.34, N 9.58.

N-Propoxy-N'-methylurea (13a)

Obtained as colourless oil, yield 90 %, ν20 1.4550. 1H NMR (300 MHz, CDCl3): δ = 0.95 (3H, t, J = 7.0 Hz, NOCH2Me), 1.67 (3H, s, J = 7.0 Hz, NOCH2Me), 2.86 (3H, br. s, Me), 3.77 (2H, t, J = 7.0 Hz, NOCH2), 5.73 (1H, s, NH), 7.61 (1H, s, NHO). Anal. Calc. for C13H19N2O2: C 67.73, H 9.24, N 21.6. N-Butyloxy-N'-(4-bromophenyl)urea (6j) and N-alkoxy-N'-alkylureas (6f-j) were obtained:

N-Benzoyloxy-N'-(2-methoxy)urea (13a)

Obtained as colourless crystals, yield 72 %, m.p. 78-79 °C. 1H NMR (400 MHz, DMSO-d6): δ = 6.90 (3H, s, Me), 3.605 (3H, s, NOME), 7.059 (2H, d, J = 8.4 Hz, C(3)H, C(5)H Ar), 7.466 (2H, d, J = 8.4 Hz, C(2)H, C(6)H Ar), 8.745 (1H, s, NH), 9.411 (1H, s, NHO). MS (FAB) m/z 181 [M+H]+ (100). Anal. Calc. for C17H16N2O2: C 59.99, H 6.71, N 15.55. Found: C 59.68, H 6.56, N 15.39.

N-Butyloxy-N'-(4-bromophenyl)urea (6j)

Obtained as colourless crystals, yield 92 %, m.p. 109-110 °C. 1H NMR (400 MHz, DMSO-d6): δ = 1.204 (3H, t, J = 7.2 Hz, NOCH2), 3.812 (2H, q, J = 7.2 Hz, NOCH2Me), 7.432 (2H, d, J = 9.2 Hz, C(2)H, C(6)H C6H4Br), 7.569 (2H, d, J = 9.2 Hz, C(3)H, C(5)H C6H4Br), 8.874 (1H, s, NH), 9.515 (1H, s, NHO). MS (FAB) m/z 261 [M+H]+ (15), 259 [M+H]+ (15), 102 (100). Anal. Calc. for C17H16BrN2O2: C 41.72, H 4.28, N 10.81. Found: C 41.59, H 4.21, N 10.56.

N-Butyloxy-N'-arylureas (6f-j)

In a similar manner, N-alkoxy-N'-aryleucras (6f-j) and N-alkoxy-N'-alkylureas (13a, b) were obtained:

N-Butyloxy-N'-arylureas (6f-j)

Preparation of cis-diastereomer, 4S,5S-dihydroxy-3-methoxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (11a)

4-Nitrophenylglyoxal hydrate (102 mg, 0.518 mmol) was added to the solution of 6e (86 mg, 0.518 mmol) in acetic acid (5 mL). The reaction mixture was maintained in a closed bulb at 20 °C for 6 days, the obtained precipitate was then filtered off, washed with dry benzene (1 mL) and dried under vacuum (2 mm Hg) to yield 6f as colourless crystals, m.p. 112–113 °C. 1H NMR (400 MHz, DMSO-d6): δ = 3.615 (3H, s, NOME), 6.984 (1H, t, J = 7.6 Hz, C(4)H Ph), 7.255 (2H, t, J = 7.6 Hz, C(3)H, C(5)H Ph), 7.575 (2H, d, J = 7.8 Hz, C(2)H, C(6)H Ph), 8.840 (1H, s, NH), 9.482 (1H, s, NHO). MS (FAB) m/z 333 [2M+H]+ (100), 167 [M+H]+ (100). Anal. Calc. for C17H16N2O2: C 57.65, H 6.26, N 16.73.

N-Butyloxy-N'-phenyleurea (6f)

In a similar manner, N-alkoxy-N'-aryleucras (6f-j) and N-alkoxy-N'-alkylureas (13a, b) were obtained:

N-Butyloxy-N'-(4-bromophenyl)urea (6j)

Obtained as colourless crystals, yield 61 %, m.p. 104-105 °C. 1H NMR (400 MHz, DMSO-d6): δ = 0.89 (3H, t, J = 7.4 Hz, NO(CH2)3Me), 1.35 (2H, sex, J = 7.4 Hz, NOCH2CH2CH2Me), 1.60 (2H, quint, J = 7.4, NOCH2CH2CH2Me), 3.76 (2H, t, J = 7.6 Hz, NOCH2), 1.47 (2H, d, J = 8.8 Hz, C(2)H, C(6)H C6H4Br), 7.56 (2H, d, J = 8.8 Hz, C(3)H, C(5)H C6H4Br), 8.85 (1H, s, NH), 9.54 (1H, s, NHO). MS (FAB) m/z 289 [M+H]+ (95), 287 [M+H]+ (100), 273 (17), 271 (17), 209 (40). Anal. Calc. for C17H16BrN2O2: C 46.01, H 5.26, N 9.76. Found: C 46.13, H 5.34, N 9.58.

N-Butyloxy-N'-phenyleurea (6f)

N-Butyloxy-N'-phenyleurea (6f)

N-Butyloxy-N'-arylureas (6f-j)

Preparation of cis-diastereomer, 4S,5S-dihydroxy-3-methoxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (11a)
3-Alkoxyl-4,5-dihydroxyimidazolin-2-ones

Section A - Research paper

**4-Nitrophenylglycolaldehyde hydrate** (176 mg, 0.893 mmol) was added to the solution of **6a** (161 mg, 0.893 mmol) in acetic acid (6 mL). The reaction mixture was stirred at 17 ºC for 23 h, then it was frozen and acetic acid was evaporated at 15 ºC under vacuum (2 mmHg), the residue was washed with water (6 mL), dried under vacuum (2 mmHg) to yield 286 mg (89 %, purity 96 %) **3-benzyloxy-4S,5S-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (11b)** as colourless crystals, m.p. 145-146 ºC (with decomp., THF-CHCl3-C6H6).

**1H NMR** (300 MHz, DMSO-d6): δ = 1.24 (3H, t, J = 6.9 Hz, NOCH2), 4.06 (2H, q, J = 6.9 Hz, NOCH2Me), 4.91 (1H, d, J = 6.6 Hz, CHOH), 7.06 (1H, t, J = 7.5 Hz, C(4)H Ph), 7.11 (1H, d, J = 6.6 Hz, CHOH), 7.21 (2H, J = 7.5 Hz, C(3)H, C(5)H Ph), 7.25 (1H, s, OH), 7.40 (2H, d, J = 7.5 Hz, C(2)H, C(6)H Ph), 7.67 (2H, d, J = 8.7 Hz, C(2)H, C(6)H CH2NO2), 8.15 (2H, d, J = 8.7 Hz, C(3)H, C(5)H CH2NO2).

**13C NMR** (75 MHz, DMSO-d6): δ = 13.97 (Me), 71.36 (NOCH2), 87.14, 87.74 (CHOH, COH), 123.29, 124.72, 125.33, 128.07, 128.31, 130.63 (C Ph, C CH2NO2), 147.25, 147.26 (C-1 Ph, C-4 CH2NO2), 156.93 (C-O). MS (FAB) m/z 360 [M+H]+ (100), 299 (28), 257 (10), 209 (100), 181 (85), 150 (40), 133 (44), 106 (25), 90 (39). Anal. Calc. for C17H17N3O6: C 59.84, H 5.78, N 10.39.

3-Benzylxylo-4S,5S-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (11c)

4-Nitrophenylglycolaldehyde hydrate (80 mg, 0.406 mmol) was added to the solution of **6f** (98 mg, 0.405 mmol) in acetic acid (5 mL), the reaction mixture was stirred at 17 ºC for 21 h, then it was frozen and acetic acid was evaporated at 16ºC under vacuum (2 mmHg), the residue was twice washed with cold water (5 mL), dried under vacuum (2 mmHg) giving 245 mg (89 %, purity 95 %) **11c** as colourless crystals, m.p. 157-159 ºC (with decomp., CH2Cl2-hexane).

**1H NMR** (400 MHz, DMSO-d6): δ = 0.90 (3H, t, J = 7.2 Hz, NOCH2), 1.615 (2H, quint, J = 0.90 Hz, 3H, CH2Ph), 2.166 (3H, s, Me), 3.948–4.046 (2H, m, NOCH2CH2CH2Me), 4.813 (1H, d, J = 8.1 Hz, C(2)H, C(3)H, C(5)H CH2NO2). **13C NMR** (75 MHz, DMSO-d6): δ = 13.78 ([CH2]3Me), 18.60 (CH2), 20.39 (CH2Me), 30.08 (CH), 75.66 (NOCH2), 87.08, 87.94 (CHOH, COH), 123.21, 125.06, 128.33, 128.80 (C-3, C-5 CH2NO2, C-3, C-5 CH2Me, C-2, C-6 CH2NO2, C-2, C-6 CH2Me), 133.33, 134.71 (C-4 CH2Me, C-1 CH2NO2), 147.24, 147.30 (C-1 CH2Me, C-4 CH2NO2), 157.00 (C-O). MS (FAB) m/z 402 [M+H]+ (12), 384 [M+H+O]+ (4), 257 (7), 251 (26), 241 (17), 235 (7), 223 (100), 195 (15), 150 (38), 133 (34), 106 (46). Anal. Calc. for C17H17N3O6: C 59.84, H 5.78, N 10.47. Found: C 59.73, H 5.86, N 10.39.

4-Butyroxy-4S,5S-4,5-dihydroxy-1-(4-methylphenyl)-5-(4-nitrophenyl)imidazolidin-2-one (11e)

4-Nitrophenylglycolaldehyde hydrate (105 mg, 0.533 mmol) was added to the solution of **6h** (119 mg, 0.533 mmol) in acetic acid (4 mL). The reaction mixture was stirred at 17 ºC for 19 h, then it was frozen and acetic acid was evaporated under vacuum (2 mmHg), the residue was twice washed with cold water (4 mL) at 4 ºC for 20 h, dried under vacuum (2 mmHg) giving 193 mg (90 %, purity 94 %) **11e** as colourless crystals, m.p. 139-141 (with decomposition, CH2Cl2-hexane).
1-(4-Bromophenyl)-3-ethoxy-4,5,5S,4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-one (11f)

4-Nitrophenylglyoxal hydrate (56 mg, 0.281 mmol) was added to the solution of 6i (73 mg, 0.281 mmol) in acetic acid (4 mL). The reaction mixture was stirred at 17°C for 22 h, then it was frozen and acetic acid was evaporated at 15°C under vacuum (2 mm Hg), the residue was twice washed with cold water (5 mL) and dried under vacuum (2 mm Hg) to yield 110 mg (89%, purity 93%) of 11f as colourless crystals, m.p. 165-166°C (with decomp., CH2Cl2-hexane). 1H NMR (300 MHz, DMSO-d6): δ = 1.23 (3H, t, J = 6.8 Hz, NOCH2Me), 4.05 (2H, q, J = 7.0 Hz, NOCH2Me), 9.10 (1H, d, J = 6.6 Hz, CHO), 7.16 (1H, d, J = 6.6 Hz, CHO), 7.35 (1H, s, OH), 7.35-7.43 (4H, m, C6H4Br), 7.76 (2H, d, J = 8.7 Hz, CHO), 8.07-8.13 (2H, d, J = 8.7 Hz, CHO), 8.28 (2H, d, J = 8.7 Hz, CHO), 3.75 (1H, s, OH), 4.12 (2H, s, CH2), 7.35–7.47 (5H, m, C 6H4Br and COH), 7.76 (2H, d, J = 8.7 Hz, CHO), 8.07-8.13 (2H, d, J = 8.7 Hz, CHO), 8.28 (2H, d, J = 8.7 Hz, CHO), 3.75 (1H, s, OH), 4.12 (2H, s, CH2), 7.35–7.47 (5H, m, C 6H4Br and COH), 7.76 (2H, d, J = 8.7 Hz, CHO), 8.07-8.13 (2H, d, J = 8.7 Hz, CHO), 8.28 (2H, d, J = 8.7 Hz, CHO), 3.75 (1H, s, OH), 4.12 (2H, s, CH2). 13C NMR (75 MHz, DMSO-d6): δ = 13.94 (Me), 71.40 (NO(CH2)Me), 87.13, 87.51 (CHOH, COH), 117.65, 123.39, 126.12, 128.20, 131.25, 135.49 (C Ar), 146.88, 147.35 (C1-C6H4NO2), 156.55 (C-O). MS (FAB) m/z 440 [M+H]+ (39), 438 [M+H]+ (39), 424 [M+H]+ (15), 245 (18), 223 (29), 182 (28), 151 (20), 141 NafCH2+ (100). Anal. Calc. for C22H21N3O6: C 50.08, H 5.67, N 13.46. Found: C 49.82, H 5.64, N 13.50.

3-Ethoxy-4,5,5S,4,5-dihydroxy-1-(1-naphthyl)methyl-5-(4-nitrophenyl)imidazolidin-2-one (14b)

A mixture of 4-nitrophenylglyoxal hydrate (134 mg, 0.680 mmol) and 13b (157 mg, 0.641 mmol) was dissolved in acetic acid (4 mL) with stirring. The reaction mixture was maintained at 16°C for 6 h, then it was filtered off and dried under vacuum (2 mm Hg) to yield 252 mg (93%, purity 93%) of 14b as yellowish solid, m.p. 155-156°C (with decomp., CH2Cl2-hexane). 1H NMR (300 MHz, DMSO-d6): δ = 1.254 (3H, t, J = 6.8 Hz, NOCH2Me), 3.98-4.13 (2H, m, NOCH2Me), 4.511 (1H, d, J = 15.0 Hz, NCH2), 4.837 (1H, d, J = 6.9 Hz, CHO), 4.918 (1H, d, J = 15.0 Hz, NCH2), 6.894-6.916 (2H, CH, CHOH, COH), 7.09-7.17 (2H, CH, CHOH), 7.321 (2H, d, J = 8.7 Hz, CHO), 7.10 (2H, s, CH2), 7.43-7.52 (3H, m, CHAr), 7.672 (2H, d, J = 8.7 Hz, CH3, C(5)H17N3O6), 7.75-7.85 (2H, CH, CHOH), 8.07-8.13 (1H, CH, CHOH). 13C NMR (75 MHz, DMSO-d6): δ = 13.78 ([CH2]Me), 18.58 (CH2), 30.04 (CH2), 75.72 (NOCH2Me), 87.12, 87.59 (CHOH, COH), 117.69 (C-4, CHO), 123.40 (C-3, C-5, CHO), 126.18, 128.24 (C-2, C-6, CHNO2), 131.26 (C-3, C-5, CHO), 135.50 (C-1, CHO), 146.89, 147.38 (C-1, CHO), 146.90 (C-4, CHO), 156.95 (CO). MS (FAB) m/z 468 [M+H]+ (19), 466 [M+H]+ (18), 450 [M+H+2O]2+ (10), 289 (100), 287 (84), 281 (85), 198 (65), 150 (94). Anal. Calc. for C4H18N3O6C 48,94, H 4.32, N 9.01. Found: C 48.75, H 4.46, N 8.96.
RESULTS AND DISCUSSION

We have found that 4-nitrophenylglyoxal with N-alkoxy-N'-aryleures (6a,e-j) in acetic acid medium at 17–20°C selectively forms 3-alkoxy-1-aryl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (11a-g), mainly as diastereomers with cis orientation of 4-HO- and 5-HO-groups (93–96%) (Scheme 7). The diastereomers 12a-g with trans orientation of 4-HO- and 5-HO-groups have been observed in the trace amounts in the reaction mixtures (1H NMR).

Scheme 7. Synthesis of 3-alkoxy-1-aryl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (11a-g, 12a-g).

Under similar conditions, 4-nitrophenylglyoxal reacts with N-propoxy-N'-methylene (13a) and N-ethoxy-N’-(1-naphthyl)methyleneurea (13b) give 3-alkoxy-1-alkyl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (14a,b) mainly as cis diastereomer (Scheme 8).

Scheme 8. Synthesis of 3-alkoxy-1-alkyl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (14a,b, 15a,b).

Firstly, the cis orientation of 4-HO- and 5-HO-groups has been proposed for the compounds 11a-j and 14a,b based on their 1H NMR spectra. For compounds 11a-j and 14a,b the doublet of CHO proton is situated in the higher field than doublet of CHOH proton of trans diastereomers 12a-j and 15a,b, as earlier it has been demonstrated for 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones 2a,b9 (Table 1).

Table 1. The characteristic 1H NMR chemical shifts of doublet of CHOH proton of 2a,b, 3a,b, 11a-g, 12a-g and 14a,b, 15a,b.

<table>
<thead>
<tr>
<th>cis Diastereomers</th>
<th>δ, ppm (J, Hz)</th>
<th>trans Diastereomers</th>
<th>δ, ppm (J, Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>4.55(7.5)</td>
<td>3a</td>
<td>4.91(5.4)</td>
</tr>
<tr>
<td>2b</td>
<td>4.52(7.2)</td>
<td>3b</td>
<td>4.84(5.7)</td>
</tr>
<tr>
<td>11a</td>
<td>4.93(6.5)</td>
<td>12a</td>
<td>5.20(5.5)</td>
</tr>
<tr>
<td>11b</td>
<td>4.91(6.6)</td>
<td>12b</td>
<td>5.18(6.0)</td>
</tr>
<tr>
<td>11c</td>
<td>4.81(6.0)</td>
<td>12c</td>
<td>5.23(6.0)</td>
</tr>
<tr>
<td>11d</td>
<td>4.92(6.4)</td>
<td>12d</td>
<td>5.19(4.8)</td>
</tr>
<tr>
<td>11e</td>
<td>4.90(6.0)</td>
<td>12e</td>
<td>5.17(3.9)</td>
</tr>
<tr>
<td>11f</td>
<td>4.90(6.8)</td>
<td>12f</td>
<td>5.17(5.7)</td>
</tr>
<tr>
<td>11g</td>
<td>4.90(6.3)</td>
<td>12g</td>
<td>5.16(5.1)</td>
</tr>
<tr>
<td>14a</td>
<td>4.71(7.8)</td>
<td>15a</td>
<td>5.04(6.0)</td>
</tr>
<tr>
<td>14b</td>
<td>4.81(7.2)</td>
<td>15b</td>
<td>5.16(6.0)</td>
</tr>
</tbody>
</table>

Figure 1. The molecular structure of 3-n-butoxy-4,5,5-dihydroxy-1-(4-methylphenyl)-5-(4-nitrophenyl)-imidazolidin-2-one (11eA), showing the atom labelling. Displacement ellipsoids are drawn with the 50% probability level according to the data X-ray structural analysis.

There are two molecules of compound 11e (11eA and 11eB) in the asymmetric part of the unit cell. Molecules 11eA and 11eB have some different structural parameters. Earlier the similar existence of compound in the two geometrical forms in the crystal was found for the N-alkoxyurea 10a10 and in other cases13-15.
The five-membered ring has an envelope conformation in both molecules. The C(2) atom deviates on 0.37 Å (11eA) and 0.53 Å (11eB) off the plain of remaining ring atoms. The N(1) atom has a pyramidal configuration. The sum of bond angles centered at the N(1) atom (Σβ) is 339.3° in molecule 11eA and 359.5° in molecule 11eB. The C(3)–OH group has equatorial orientation relative to five-membered ring (the torsion angle N(1)–C(2)–C(3)–O(3) is 97.0(5)° (molecule 11eA), -87.9(6)° (molecule 11eB)). The C(2)–OH group has equatorial orientation to five-membered ring (the torsion angle C(1)–N(1)–C(2)–O(2) is 143.7(5)° (molecule 11eA), 154.6(5)° (molecule 11eB)).

The 4-nitrophenyl substituent has equatorial orientation to five-membered ring [the torsion angle N(1)–C(2)–C(3)–(C)–C(4) is -142.0(5)° (molecule 11eA), 152.3(5)° (molecule 11eB)]. It is rotated relatively to the C(2)–C(3) endocyclic bond [the torsion angle C(2)–C(3)–(C)–C(4)–C(9) is 75.8° (molecule 11eA), 104.4° (molecule 11eB)]. The nitro group is slightly rotated towards the plane of the aromatic cycle [the torsion angle C(6)–C(7)–N(3)–O(4) is 7.2(6)° (molecule 11eA), -15.4(2)° (molecule 11eB), the torsion angle C(8)–C(7)–N(3)–O(5) is -0.3(1)° (molecule 11eA), -18.6(9)° (molecule 11eB)].

In the compound 11e the ordinary bonds O(2)–C(2) and O(3)–C(3) are in some way different: the O(3)–C(3) bond [1.399(6) Å (11eA), 1.405(6) Å (11eB)] is little bit longer than the O(2)–C(2) bond [1.380(7) Å (11eA), 1.369(7) Å (11eB)]. The similar bond difference was found for 5-aryl-4,5-dihydroxyimidazolin-2-ones [1.398(7) Å in compound 2a, 1.399(6) Å in molecule 11eA, 1.410(6) Å (11eB)] is similar to the same bond's lengths in compounds 2a, b [1.398(7) Å in compound 2a, 1.405(1) Å in compound 2b].

The butyloxy group has +ac-configuration to the endocyclic C(2)–N(1) bond in the molecule 11eA and –ac-configuration in the molecule 11eB [the torsion angle C(2)–N(1)–O(6)–C(17) is 121.3(6)° (molecule 11eA), -107.6(6)° (molecule 11eB)]. It has tandem conformation [the torsion angle N(1)–O(6)–C(17)–C(18) is -179.0(7)° (molecule 11eA), 170.1(6)° (molecule 11eB), the torsion angle O(6)–C(17)–C(18)–C(19) is 171.7(1)° (molecule 11eA), -159.4(1)° (molecule 11eB)].

In the crystal, the molecules 11eA and 11eB are linked into dimers by the intermolecular hydrogen bond O(3B)–H(3B)...O(1A)° (x, y, z) (H...O 1.87 Å, O–H...O 167°). These dimers form the chains toward crystallographic direction [0 0 1] due to intermolecular hydrogen bonds O(3A)–H(3A)...O(2A)° (1-x, 1-y, -z) (H...O 2.23 Å, O–H...O 148°) and O(3B)–H(3B)...O(1A)° (x, y, z) (H...O 0.187 Å, O–H...O 167°).

The molecular structure 4S,5S,4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propoxyimidazolidin-2-one (14a) is very similar to the molecular structure of compound 11e.

There are two molecules of 4S,5S,4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propoxyimidazolidin-2-one (14a) (14aA and 14aB) in the asymmetric part of the unit cell. These molecules have different structural parameters.

Figure 2. Molecular structure of 4S,5S,4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propoxyimidazolidin-2-one (14aA) with atoms represented by thermal vibration ellipsoids of 50% probability level according to the data of X-ray structural analysis.

The five-membered ring has an envelope conformation in both molecules. The C(3) atom deviation of the plane of the remaining ring atoms is 0.42 Å in the molecule 14aA and 0.46 Å in the molecule 14aB. The nitrogen atom N(1) has the planar configuration (Σβ=356° in the molecule 14aA and Σβ=357° in the molecule 14aB). The nitrogen atom N(2) has the pyramidal configuration (Σβ=337.4° in the molecule 14aA and Σβ=336° in the molecule 14aB). The hydroxyl group at the C(2) atom has an axial orientation to the five-membered ring (the C(1)–N(2)–C(3)–O(3) torsion angle is -146.2(7)° (14aA), 152.1(7)° (14aB)).

The 4-nitrophenyl substituent is equatorially oriented to the five-membered ring [the torsion angle N(2)–C(3)–C(5) is 147.6(6)° (14aA), -150.6(7)° (11eB)]. It is rotated towards the C(2)–C(3) endocyclic bond (the torsion angle C(3)–C(2)–C(5)–C(6) is 68.6° (14aA), 74.4° (14aB)]. The nitro group is slightly rotated towards the plane of the aromatic cycle (the torsion angle C(7)–C(8)–N(3)–O(5) is -2.8(2)° (14aA), 10.5(2)° (14aB), the torsion angle C(9)–C(8)–N(3)–O(4) is -4.9(2)° (14aA), 5.4(1)° (14aB)].

In the compound 14a the ordinary bonds O(4)–C(2) and O(3)–C(3) are in some way different: the O(4)–C(2) bond [1.427(8) Å (14aA), 1.431(9) Å (14aB)] is longer than the O(3)–C(3) bond [1.381(9) Å (14aA), 1.387(9) Å (14aB)]. The similar bond difference takes place in the compounds 2a, b, 11e. The length of O(2)–N(2) bond [1.420 (8) Å (14aA), 1.418 (8) Å (14aB)] is similar to the same bond's length in the compound 11e. The propoxy group has –ac-configuration to the endocyclic C(3)–N(2) bond in the molecule 14aA and +ac-configuration in the molecule 14aB (the torsion angle C(3)–N(2)–O(2)–C(11) is 106.8° (14aA), 115.8(8) (14aB)). It has tandem conformation (the torsion angle N(2)–O(2)–C(11)–C(12) is 175.8° (14aA), 175.5(9)° (14aB), the torsion angle O(2)–C(11)–C(12)–C(13) is -174.2(9)° (14aA), -179.0(1)° (14aB)].

In the crystal molecules 14aA and 14aB are linked in the dimers by the intermolecular hydrogen bond O(3B)–H(3B)...O(1A)° (x, y, z) (H...O 1.98 Å, O–H...O 167°). These dimers form the chains toward crystallographic direction [0 1 0] due to intermolecular hydrogen bonds O(3A)–H(3A)...O(4B)° (x, -1+y, -z) (H...O 2.06 Å, O–H...O 178°) and O(4A)–H(4A)...O(2A)° (1.5-x, 0.5+y, 2+z) (H...O 2.12 Å, O–H...O 136°) (Figure 3).
further transformation of the compounds \(-\text{alkoxy}-\)N-Eur. Chem. Bull., the proposed mechanism of the interaction of 4-Scheme 9. Figure 3. The rearrangement molecules 14A and 14AB in the crystal according to the data of X-ray structural analysis. For the studied reaction of arylglyoxals with N-hydroxyurea,\(^7\)\(^9\) N-alkoxy-N’-aryleureas\(^10\) and N-alkoxy-N’-alkylureas a possible mechanism results dominating the formation of the diastereomers with cis orientation of 4-HO- and 5-HO-groups has been proposed (Scheme 9). At the first stage, the open-chain N-alkoxyurea 16A is formed which has intramolecular hydrogen bond. The intermediate 16A can isomerize into the enolic form 16B possessing the same intramolecular hydrogen bond. In the further cyclization of intermediate 16A (route I Scheme 9), or intermediate 16B (route II Scheme 9) yields the diastereomer with cis orientation of 4-HO- and 5-HO-groups due to presence of this intramolecular hydrogen bond. The mild conditions of the reaction (no heating) preserve the further isomerization of the forming cis diastereomers 11, 14 into trans diastereomers 12, 15.

Conclusions
4-Nitrophenylglyoxal reacts with N-alkoxy-N’-aryleureas (6A-e-i) and N-alkoxy-N’-alkylureas (13A-b) in acetic acid medium at the room temperature forming mainly 3-alkoxy-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-one (11a-g) and 3-alkoxy-1-alkyl-4,5-dihydroxy-5-(4-nitrophenyl)-imidazolidin-2-one (14a-b), respectively, which have cis oriented hydroxy groups. X-Ray structural analysis of 3-n-butylxy-4S,5S-4,5-dihydroxy-1-(4-methylphenyl)-5-(4-nitrophenyl)imidazolidin-2-one (11c) and 4S,5S-4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propoxyimidazo-lidin-2-one (14a) has confirmed this special structural feature of these compounds.

References

\[ \text{Substituted 3-alkoxy-4,5-dihydroimidazolin-2-ones} \]


