THE PECULIARITIES OF THE 4-CARBOXYPHENYLGLYOXAL AND *N*-ALKOXY-*N'*-ARYLUREAS INTERACTION

Vasiliy G. Shtamburg,[a]* Victor V. Shtamburg,[a] Andrey A. Anishchenko[b] and Alexander V. Mazepa[c]

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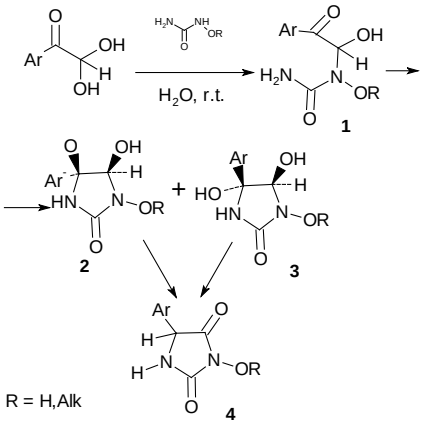
It was found that 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones are the only products of interaction of *N*-alkoxyureas with arylglyoxals which have strong electronegative substituent in the forth position of the aryl moiety. The possibility of obtaining such products as 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones, 3-alkoxy-1-alkyl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones and 3-alkoxy-1-phenyl-4,5-dihydroxy-5-(4-nitrophenyl)-imidazolidin-2-ones has been verified in the experimental way. In most the cases 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones were produced as a mixture of diastereomers.

*Corresponding Authors
Fax: +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 Dnipro National University.
[c] 65080 Odessa, Luystdorfskaya Doroga st., 86. A.V. Bogatsky Physico-Chemical Institute of NAS of Ukraine.

INTRODUCTION

As it was shown in our previous publications[1-6] the arylglyoxals' interaction with *N*-hydroxyurea and *N*-alkoxyureas is a very promising way to get valuable pharmaceutical materials. Three types of products can be produced by this reaction. As we have shown some of the products transform into others.

The following products can be obtained from this reaction: substituted ureas **1**, diastereomers of 3,4,5-trihydroxy-5-arylimidazolidin-2-ones, 3-alkoxy-4,5-dihydroxy-5-arylimidazolidin-2-ones **2** and **3** respectively, or 3-hydroxy- or 3-alkoxyhydantoins **4**.



Scheme 1. The products of interaction of arylglyoxals with *N*-hydroxyurea or *N*-alkoxyureas.

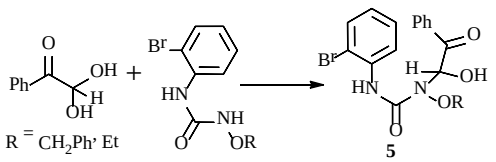
The mechanism of this interaction could not be completely established because of lack of experimental evidence. In any case the formation pattern of each product type is valuable. It is important to know this pattern not only in order to determine the reaction mechanism, but also to get further perspective synthones and materials in pharmacy, organic synthesis and bioorganic chemistry.

The relevance of the products which can be obtained by the interaction of arylglyoxals with *N*-hydroxyurea or *N*-alkoxyureas is significant because of the importance of imidazolidin-2-ones and imidazolidin-2,4-diones among pharmaceutical materials.[7-10] Arylglyoxals are widely used in synthesis of these biologically active nitrogen-containing heterocycles.[11]

Despite the differences between the products of the arylglyoxals interaction with *N*-hydroxyurea or *N*-alkoxyureas we have observed several patterns in their formation. In fact, the type of the product strongly depends on the glyoxal reagent. However, when we use arylglyoxals with electron-donating groups in aryl moiety, the substituted ureas **1** might be not the only products of this reaction.[1] As usual the first type products, substituted ureas **1,** forms imidazolidin-2-ones **2** and **3**, which further turns into hydantoins **4**. Nevertheless, it is possible to obtain only the substituted ureas **5** in this interaction.[2,6] For this result the strong intramolecular effects should take place in the compounds **5** (Scheme 2).

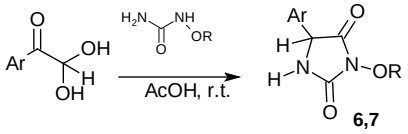
The mixture of the second type products, 4,5-dihydroxyimidazolidin-2-ones **2** and **3**, and the third type of products, hydantoins **4**, are obtained in all the other cases. This fact serves as clear evidence that the cyclization of substituted ureas into 5-arylimidazolidin-2-ones is an easy process. This process could be retarded by intramolecular effect or steric factor.[1,2,4-6]

Very often the second type products, 4,5-dihydroxyimidazolidin-2-ones **2** and **3**, turn into third type products, hydantoins **4,**[1,6] but not always.



Scheme 2. Formation of the substituted ureas as the only product in the interaction of arylglyoxals with *N*-alkoxyureas.

For now the most convenient method of getting only the third type product is using acetic acid as a solvent for the reaction of arylglyoxals with *N*-hydroxyurea or *N*-alkoxyureas.[3] The products are only 3-hydroxyhydantoines **6** or 3-alkoxyhydantoines **7** respectively (Scheme 3).

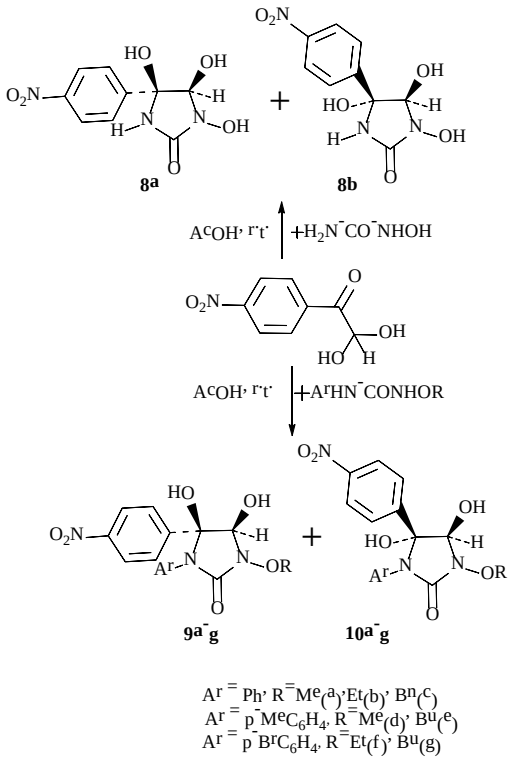


Ar = p-XC_6H_4, X = H (a), F(b), Cl(c), Br(d)

R=H(**6**), Me, Et, Bu(**7**)

Scheme 3. The products of interaction of arylglyoxals with *N*-hydroxyurea or *N*-alkoxyureas in acetic acid.

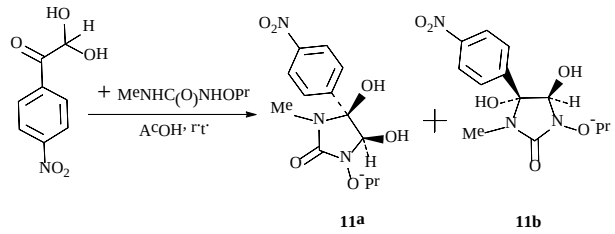
Only the second type products were formed in the reactions of 4-nitrophenylglyoxal with *N*-hydroxyurea[4] or *N*-alkoxy-*N*-arylureas.[5] In fact 4-nitrophenylglyoxal reacts with *N*-hydroxyurea producing only the mixture of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones **8a** and **8b** in molar ratio approximately 3:1[4] (Scheme 4).



Scheme 4. The products of 4-nitrophenylgyoxal interaction with *N*-hydroxyurea[4] and *N*-alkoxy-*N'*-arylureas.[5]

Also, 4-nitrophenylglyoxal reacts with *N*-alkoxy-*N'*-arylureas in acetic acid at room temperature mainly producing 3-alkoxy-1-aryl-4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones **9a-g**[5] (Scheme 4). These compounds have 4-hydroxyl and 5-hydroxyl groups in the *cis*-conformation to each other.

It was shown that the reaction of 4-nitrophenylglyoxal with *N*-*n*-propyloxy-*N'*-methylurea in acetic acid leads mainly to the formation of 3-*n*-propyloxy-1-methyl-4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-one **11a** (**11a**:**11b**=99:1)[5] (Scheme 5).



Scheme 5. The products of 4-nitrophenylgyoxal interaction with *N*-*n*-propyloxy-*N'*-methylurea[5].

The diastereomers of 5-aryl-4,5-dihydroxyimidazolidin-2-one **8a**,**9a**,**11a** with *cis* orientation of 4-HO- and 5-HO-groups to each other prevailed over the *trans* isomers for all the experiences.

To sum up all the information about arylglyoxals interaction with *N*-hydroxyurea derivatives we should note that the experimental investigation of the second type product formation overall pattern needed to be continued. For this reason we have chosen to explore the reaction of 4-carboxyphenylglyoxal with different *N*-alkoxy-*N'*-arylureas in acetic acid medium and for at least one case to change this alkoxyurea's reagent to the one of the *N*-alkoxy-*N'*-alkylureas.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXP-300 spectrometer (300 MHz) and VARIAN VNMRS 400 spectrometer (400 MHz). ^{13}C NMR spectra were recorded on a Varian VXP-300 spectrometer (75 MHz). The solvents DMSO-d_6 and $CDCl_3$ were used. ^{1}H NMR chemical shifts relative to the residual solvent protons as an internal standard [$(CD_3)_2SO$: 2.500 ppm, $CDCl_3$: 7.260 ppm] were reported. Solvent carbon atoms served as an internal standard for ^{13}C NMR spectra [$(CD_3)_2SO$: 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 the standard procedure[4] by oxidation of 4-nitroacetophenone with H_2SeO_3 in boiling acetic acid for 2h, then removing AcOH under vacuum and crystallization of the residue from boiling water, as yellow powder, m.p. 87–89 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.66 (1H, t, *J* = 6.8, C<u>H</u>(OH)$_2$), 7.03 (2H, d, *J* = 6.8, CH(O<u>H</u>)$_2$), 8.29 (2H, d, *J* = 9.2, H Ar), 8.34 (2H, d, *J* = 9.2, H Ar).

4-Carboxyphenylglyoxal hydrate was obtained according to the similar standard procedure[4] by oxidation 4-acetylbenzoic acid oxidation by H_2SeO_3 in boiling acetic acid for 3h, then removing AcOH under vacuum and crystallization of the residue from boiling water, as an unstable pink powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.672 (1H, s, CH), 6.885 (2H, br. s, OH), 8.051 (2H, d, ^3J = 8.0 Hz, Ar), 8.161 (2H, d, ^3J = 8.0 Hz, Ar), 13.321 (1H, br. s, COOH).

_N-n_-Butyloxy-_N'_-phenylurea

A solution of phenylisocyanate (1.240g, 10.413 mmol) in benzene (5 mL) was added to a solution of *n*-butyloxyamine (0.975 g, 10.933 mmol) in benzene (8 mL), the reaction mixture was kept at 60 ºC for 30 min, then the solvent was evaporated under vacuum (20 mmHg) and hexane (8 mL) was added. After keeping at -5ºC for 20 h the obtained precipitate was filtered off, washed by cold (-5ºC) hexane, dried under vacuum (5 mmHg), giving 1.843 g (85 %) of *N-n*-butyloxy-*N'*-phenylurea, colorless crystals, m.p. 77–79 ºC. ^{1}HNMR (300 MHz, DMSO-d_6): δ = 0.900 (3H, t, ^3J = 7.5 Hz, NO(CH$_2$)$_3$Me), 1.356 (2H, sex, ^3J = 7.5 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.608 (2H, quint, ^3J = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$Me), 3.765 (2H, t, ^3J = 7.2 Hz, NOCH$_2$), 6.983 (1H, t, ^3J = 7.8 Hz, C(4)H Ph), 7.257 (2H, t, ^3J = 7.8 Hz, C(3)H, C(5)H Ph), 7.551 (2H, t, ^3J = 7.8 Hz, C(2)H, C(6)H Ph), 8.665 (1H, s, NH), 9.431 (1H, s, NHO). MS (FAB) m/z 209 [M+H]$^+$ (100). Calc. for $C_{11}H_{16}N_2O_2$: C 63.44, H 7.74, N 13.45. Found: C 63.31, H 7.56, N 13.15.

3-_n_-Butyloxy-4,5-dihydroxy-5-(4-carboxyphenyl)-1-phenylimidazolidin-2-one (12)

4-Carboxyphenylglyoxal hydrate (71.2 mg, 0.3634 mmol) was added to the solution of *N-n*-butyloxy-*N'*-phenylurea (75.9 mg, 0.364 mmol) in acetic acid (5 mL), the reaction mixture was stirred for 29 h at 22 °C, then the negligible precipitate was filtered off, the filtrate was evaporated under vacuum (4 mmHg) at 20 °C, the residue was washed by water and dried under vacuum (4 mmHg), giving 134 mg (91 %) of monohydrate of 3-*n*-butyloxy-4,5-dihydroxy-5-(4-carboxyphenyl)-1-phenylimidazolidin-2-one **12**, colorless crystals, m.p. 108–111 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.899 (3H, t, ^3J = 7.2 Hz, NO(CH$_2$)$_3$Me), 1.399 (2H, sex, ^3J = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.611 (2H, quint, ^3J = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$Me), 3.999 (2H, t, ^3J = 6.0 Hz, NOCH$_2$), 4.856 (1H, d, ^3J = 6.3 Гц, CHOH), 6.987–7.082 (3H, m, OH, CHOH и C(4)H Ph), 7.188 (2H, t, ^3J = 7.5 Hz, C(3)H, C(5)H Ph), 7.385 (2H, d, ^3J = 7.5 Hz, C(2)H, C(6)H Ph), 7.586 (2H, d, ^3J = 8.4 Hz, C(2)H, C(6)H C$_6$H$_4$), 7.855 (2H, d, ^3J = 8.4 Hz, C(3)H, C(5)H C$_6$H$_4$), 12.977 (1H, s, COOH). ^{1}H NMR (300 MHz, CD$_3$CN): δ = 0.938 (3H, t, ^3J = 7.35 Hz, NO(CH$_2$)$_3$Me), 1.440 (2H, sex, ^3J = 7.35 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.663 (2H, quint, ^3J = 7.1 Hz, NOCH$_2$CH$_2$CH$_2$Me), 4.031 (2H, t, ^3J = 6.1 Hz, NOCH$_2$), 4.975 (1H, s, CHOH), 7.095 (1H, t, ^3J = 7.5 Hz, C(4)H Ph), 7.214 (2H, t, ^3J = 7.5 Hz, C(3)H, C(5)H Ph), 7.387 (2H, d, ^3J = 7.5 Hz, C(2)H, C(6)H Ph), 7.619 (2H, d, ^3J = 8.4 Hz, C(2)H, C(6)H C$_6$H$_4$), 7.914 (2H, d, ^3J = 8.4 Hz, C(3)H, C(5)H C$_6$H$_4$). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.87 (Me), 18.66 (CH$_2$), 30.14 (CH$_2$), 75.67 (NOCH$_2$), 87.35 (CHOH), 88.12 (COH), 124.71, 125.19, 127.01, 128.26, 129.29, 130.53, 136.29 (C Ar), 144.83 [C(1) PhN], 157.05 [NC(=O)N], 166.99 (COOH). MS (FAB) m/z 387 [M+H]$^+$ (22), 369 [M+H–H$_2$O]$^+$ (9), 250 (26), 209 (100), 149 (49). Anal. Calc. for $C_{20}H_{22}N_2O_6$.H$_2$O, %: C 59.40, H 5.98, N 6.93. Found, %: C 59.07, H 6.13, N 6.85.

4,5-Dihydoxy-5-(4-carboxyphenyl)-3-methoxy-1-(4-methylphenyl)imidazolidin-2-one (13)

4-Carboxyphenylglyoxal hydrate (97.9 mg, 0.499 mmol) was added to the solution of *N*-methoxy-*N'*-4-methylphenylurea[5] (89.9 mg, 0.499 mmol) in acetic acid (8 mL), the reaction mixture was stirred for 38 h at 20 °C, then the negligible precipitate was filtered off and the filtrate was evaporated under vacuum (2 mmHg) at 20 °C, yielding 175 mg (93 %) the mixture of the diastereoisomers **13a** and **13b** in molar ratio 91:9 (^{1}HNMR spectrum). This mixture was extracted by water (4 mL) at 4°C for 23 h, the obtained precipitate was filtered off and dried under vacuum giving 118 mg (63 %) of monohydrate of 4,5-dihydroxy-5-(4-carboxyphenyl)-3-methoxy-1-(4-methylphenyl)imidazolidin-2-one **13a**, white solid, mp. 81–83 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.164 (3H, s, Me), 3.817 (3H, s, NOMe), 4.891 (1H, d, ^3J = 5.4 Hz, CHOH), 6.991 (2H, d, ^3J = 8.7 Hz, C(3)H, C(5)H C$_6$H$_4$Me), 7.017–7.076 (2H, m, CHOH and OH), 7.241 (2H, d, ^3J = 8.7 Hz, C(2)H, C(6)H C$_6$H$_4$Me), 7.577 (2H, d, ^3J = 8.1 Hz, C(2)H, C(6)H C$_6$H$_4$COOH), 7.842 (2H, d, ^3J = 8.1 Hz, C(3)H, C(5)H C$_6$H$_4$COOH), 12.952 (1H, br. s, COOH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.40 (Me), 63.95 (NOMe), 87.23 (CHOH), 87.90 (COH), 125.13, 127.00, 128.70, 129.08, 130.45, 133.41, 134.63 (C Ar), 144.67 [C(1) C$_6$H$_4$Me, C–N], 156.92 (NC(=O)N), 166.90 (COOH). MS (FAB) m/z 359 [M+H]$^+$ (41), 341 [M+H–H$_2$O]$^+$ (10), 256 (7), 238 (9), 208 (100), 181 (37), 149 (76), 133 (28), 121 (8), 106 (19). Calc. for $C_{18}H_{18}N_2O_6$.H$_2$O, %: C 57.44, H 5.35, N 7.44. Found, %: 55.78, H 5.54, N 7.42.

5-(4-Carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxy-imidazolidin-2-one (14)

4-Carboxyphenylglyoxal hydrate (74.6 mg, 0.380 mmol) was added to a solution of *N*-propyloxy-*N'*-methylurea[5] (55.7 mg, 0.421 mmol) in acetic acid (5 mL). The reaction mixture was stirred for 26 h at 22 °C, then the negligible precipitate was filtered off and the filtrate was evaporated under vacuum (2 mmHg) at 20 °C. The residue was dissolved in water (5 mL), the aqueous solution was filtered and evaporated under vacuum (2 mmHg) at 20 °C. The obtained residue was washed by Et$_2$O (2 mL) and dried under vacuum (2 mmHg), yielding 104 mg (84 %) of monohydrate of 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one **14**, colorless crystals, m.p. 124–127 °C (with decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.898 (3H, t, ^3J = 7.2 Hz, NO(CH$_2$)$_2$Me), 1.597 (2H, sex, ^3J = 6.9 Hz, NOCH$_2$CH$_2$Me), 2.465 (3H, s, NMe), 3.831–3.910 (2H, m, NOCH$_2$), 4.645 (1H, d, ^3J = 7.8 Hz, CHOH), 6.569 (1H, s, OH), 6.609 (1H, d, ^3J = 7.8 Hz, CHOH), 7.529 (2H, d, ^3J = 8.7 Hz, C(2)H, C(6)H C$_6$H$_4$COOH), 7.970 (2H, d, ^3J = 8.7 Hz, C(3)H, C(5)H C$_6$H$_4$COOH), 12.997 (1H, br. s, COOH). ^{13}C NMR (75 MHz, DMSO-d_6): δ =10.35 (Me), 21.39 (CH$_2$), 25.17 (NMe), 77.44 (NOCH$_2$), 85.97 (CHOH), 88.63 (COH), 126.76, 129.50 [C(H) C$_6$H$_4$], 130.75 [C(4) C$_6$H$_4$], 144.62 [C(1) C$_6$H$_4$, C–N], 158.94 [NC(=O)N], 167.08 (COOH). MS (FAB) m/z

311 $[M+H]^+$ (77), 293 $[M+H-H_2O]^+$ (36), 235 (83), 209 (59), 149 (100). Anal. Calc. for $C_{14}H_{18}N_2O_6.H_2O$ %: C 51.22, H 6.14, N 8.53. Found, %: 50.98, H 6.35, N 8.26.

N-*n*-Octyloxy-*N*'-phenylurea

A solution of phenylisocyanate (0.714 g, 5.994 mmol) in benzene (5 mL) was added to a solution of *n*-octyloxyamine (0.959 g, 6.600 mmol) in benzene (5 mL). The reaction solution was maintained at 20 °C for 72 h, then benzene was evaporated under vacuum (20 mmHg), hexane (11 mL) was added to the residue and the obtained mixture was kept at -5°C for 20 h. The formed precipitate was filtered off, washed by hexane (6 mL) and dried under vacuum (2 mmHg), giving 1.335 (84 %) of *N*-*n*-octyloxy-*N*'-phenylurea, colorless crystals, m.p. 73–75 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 0.854 (3H, t, ^3J = 6.9 Hz, $NO(CH_2)_7\underline{Me}$), 1.217–1.378 (10H, m, $NOCH_2CH_2(\underline{CH_2})_5Me$), 1.614 (2H, quint, ^3J = 6.9 Hz, $NOCH_2\underline{CH_2}(CH_2)_5Me$), 3.751 (2H, t, ^3J = 6.9 Hz, $NOCH_2$), 6.982 (1H, t, ^3J = 8.1 Hz, C(4)H Ph), 7.253 (2H, t, ^3J = 8.1 Hz, C(3)H,C(5)H Ph), 7.546 (2H, d, ^3J = 8.1 Hz, C(2)H,C(6)H Ph), 8.660 (1H, s, NH), 9.421 (1H, s, NHO). MS (FAB) m/z 265 $[M+H]^+$ (100). Anal. Calc. for $C_{15}H_{24}N_2O_2$ %: C 68.15, H 9.15, N 10.60. Found, %: C 67.98, H 9.27, N 10.32.

N-*n*-Dodecyloxy-*N*'-phenylurea

A solution of phenylisocyanate (0.596 g, 5.003 mmol) in benzene (2 mL) was added to a solution of *n*-dodecyloxyamine (1.007 g, 5.001 mmol) in benzene (8 mL). The reaction solution was maintained at 20 °C for 95 h, after that it was boiled 0.5 h, then the benzene evaporated under vacuum (20 mmHg), hexane (8 mL) was added to the residue and the obtained mixture was maintained at -5°C for 20 h. The formed precipitate was filtered off, washed by hexane (6 mL) and dried under vacuum (2 mmHg) giving 1.345 (83.9 %) of *N*-*n*-dodecyloxy-*N*'-phenylurea, colorless crystals, m.p. 50–51°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.880 (3H, t, ^3J = 6.8 Hz, $NO(CH_2)_{11}\underline{Me}$), 1.221–1.449 (18H, m, $NOCH_2CH_2(\underline{CH_2})_9Me$), 1.706 (2H, quint, ^3J = 6.8 Hz, $NOCH_2\underline{CH_2}(CH_2)_9Me$), 3.915 (2H, t, ^3J = 6.8 Hz, $NOCH_2$), 7.100 (1H, t, ^3J = 8.0 Hz, C(4)H Ph), 7.329 (2H, t, ^3J = 8.0 Hz, C(3)H,C(5)H Ph), 7.470 (2H, dd, ^3J = 8.0 Hz, J = 0.8 Hz, C(2)H,C(6)H Ph), 7.566 (1H, s, NH). MS (FAB) m/z 321 $[M+H]^+$ (100). Anal. Calc. for $C_{19}H_{32}N_2O_2$, %: C 88.06, H 10.06, N 8.74. Found, %: C 87.95, H 10.11, N 8.65.

4,5-Dihydroxy-5-(4-nitrophenyl)-3-*n*-octyloxy-1-phenylimidazolidin-2-one (15)

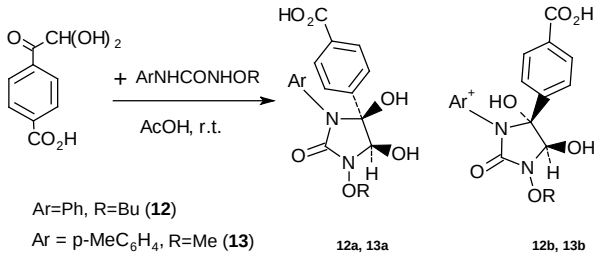
4-Nitrophenylglyoxal hydrate (87 mg, 0.441 mmol) was added to a solution of *N*-*n*-octyloxy-*N*'-phenylurea (116.6 mg, 0.441 mmol) in acetic acid (5 mL) with stirring. The reaction solution was maintained at 10 °C for 22 h, then acetic acid was evaporated under vacuum (2 mmHg) at 25 °C. Water (3 mL) was then added to the obtained residue, this mixture was maintained at 10°C for 20 h and then water was evaporated under vacuum (2 mmHg) at 25 °C yielding 196 mg (97 %) the mixture of *cis*-4,5-dihydroxydiastereomer **15a** and *trans*-4,5-dihydroxy-diastereomer **15b** (in the ratio 97:3) of 4,5-dihydroxy-5-(4-nitrophenyl)-3-*n*-octyloxy-1-phenylimidazo-lidin-2-one **15**. The pure 4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)-3-*n*-octyloxy-1-phenylimidazolidin-2-one **15a** was obtained by crystallization (benzene-hexane), colorless crystals, m.p. 53–54 °C (PhH–C_6H_{14}). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.851 (3H, t, ^3J = 6.3 Hz, $NO(CH_2)_7\underline{Me}$), 1.178–1.329 (10H, m, $NOCH_2CH_2(\underline{CH_2})_5Me$), 1.563–1.680 (2H, m, $NOCH_2\underline{CH_2}(CH_2)_5Me$), 3.944–4.021 (2H, m, $NOCH_2$), 4.887 (1H, d, ^3J = 5.4 Hz, $\underline{CH}OH$), 7.048 (1H, d, ^3J = 5.4 Hz, $CHO\underline{H}$), 7.083 (1H, t, ^3J = 8.0 Hz, C(4)H Ph), 7.203 (2H, t, ^3J = 8.0 Hz, C(3)H,C(5)H Ph), 7.275 (1H, s, OH), 7.390 (2H, d, ^3J = 7.8 Hz, C(2)H,C(6)H Ph), 7.762 (2H, d, ^3J = 8.4 Hz, C(2)H,C(6)H $C_6H_4NO_2$), 8.151 (2H, d, ^3J = 8.4 Hz, C(3)H,C(5)H $C_6H_4NO_2$). ^{13}CNMR (75 MHz, DMSO-d_6): δ =13.93 (Me), 22.12, 25.38, 28.03, 28.68, 28.87, 31.26 (CH_2), 75.98 ($NOCH_2$), 87.14 (CH–OH), 87.81 (C–OH), 119.48, 123.25, 124.65, 125.26, 128.26, 128.27, 136.05 (C Ar), 147.29 [C(4) $C_6H_4NO_2$], 156.86 (C=O). MS (FAB) m/z 444 $[M+H]^+$ (11), 307(18), 265(87), 195(37), 150(61), 120(43), 76(48), 70(40), 55(100).

3-*n*-Dodecyloxy-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (16)

4-Nitrophenylglyoxal hydrate (105 mg, 0.533 mmol) was added to a solution of *N*-*n*-dodecyloxy-*N*'-phenylurea (171 mg, 0.533 mmol) in acetic acid (4 mL) with stirring. The reaction mixture was stirred at 16 °C for 1 h, maintained at 16°C for 23 h, then acetic acid was evaporated under vacuum (2 mmHg) at 16°C. The obtained residue was washed by water (10 mL) at 6°C for 18 h, the formed precipitate was filtered off, washed by water (10 mL) and dried under vacuum (2 mmHg) to give 263 mg (95 %) mixture of *cis*-4,5-dihydroxydiastereomer **16a** and *trans*-4,5-dihydroxydiastereomer **16b** in the ratio 89:11 (^{1}H NMR). Crystallization of this mixture from CH_2Cl_2–hexane yields 3-*n*-dodecyloxy-4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one **16a**, colorless crystals, m.p. 98-100 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.844 (3H, t, ^3J = 6.2 Hz, $NO(CH_2)_{11}\underline{Me}$), 1.174–1.426 (18H, m, $NOCH_2CH_2(\underline{CH_2})_9Me$), 1.564–1.685 (2H, m, $NOCH_2\underline{CH_2}(CH_2)_9Me$), 3.929–4.033 (2H, m, $NOCH_2$), 4.888 (1H, s, $\underline{CH}OH$), 7.041 (1H, s, $CHO\underline{H}$), 7.079 (1H, t, ^3J = 7.5 Hz, C(4)H Ph), 7.201 (2H, t, ^3J = 7.5 Hz, C(3)H,C(5)H Ph), 7.265 (1H, s, OH), 7.395 (2H, d, ^3J = 7.5 Hz, C(2)H,C(6)H Ph), 7.762 (2H, d, ^3J = 8.7 Hz, C(2)H,C(6)H $C_6H_4NO_2$), 8.151 (2H, d, ^3J = 8.7 Hz, C(3)H,C(5)H $C_6H_4NO_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ =13.99 (Me), 22.14, 25.38, 28.04, 28.76, 28.92, 28.93, 29.05, 29.07, 29.11, 31.34 (CH_2), 75.97 ($NOCH_2$), 87.15 (CH–OH), 87.80 (C–OH), 123.30, 124.16, 124.70, 125.32, 128.29, 128.32, 136.0 (C Ar), 147.28 [C(4) $C_6H_4NO_2$], 156.87 (C=O). MS (FAB) m/z 500 $[M+H]^+$ (13), 482 $[M+H-H_2O]^+$ (6), 363 (22), 321 (100), 243 (15), 194 (54), 150 (44), 120 (67).

RESULTS AND DISCUSSION

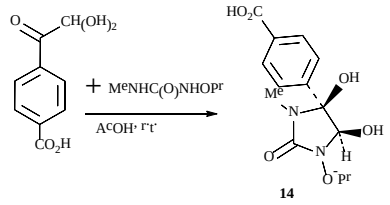
We found that *N*-alkoxy-*N*'-arylureas react with 4-carboxyphenylglyoxal in acetic acid medium at room temperature yielding the mixtures of diastereomers of 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazo-lidin-2-ones **12**,**13** (Scheme 6).



Scheme 6. The products of interaction of 4-carboxyphenylglyoxal with *N*-alkoxy-*N'*-arylureas.

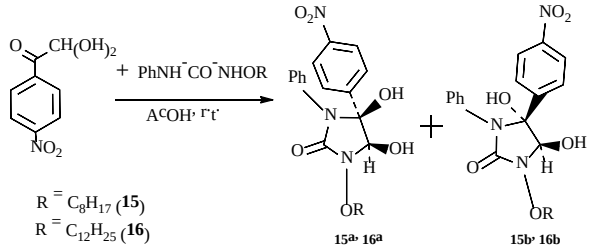
We assume, in the interaction of 4-nitrophenylgyoxals with *N*-alkoxy-*N'*-arylureas,[5] that the main product in both cases is similar. In the last case it is the diastereomer **12a** or **13a** with 4-hydroxyl- and 5-hydroxyl groups in the *cis*-conformation to each other. Their percentage in the products' mixtures is approximately 91-98 %.

In a similar way the *N*-propyloxy-*N'*-methylurea's interaction with 4-carboxyphenylglyoxal produces only 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxy-imidazolidin-2-one **14** (Scheme 7). In this interaction the only one diastereomer **14** is formed. It became clear that it has *cis* orientation of 4-HO- and 5-HO-groups in the *cis*-conformation to each other. So, the result is similar to the 4-nitrophenylgyoxal's interaction with *N*-propyloxy-*N'*-methylurea[5].



Scheme 7. Interaction of 4-carboxyphenylglyoxal with *N*-propyloxy-*N'*-methylurea.

Thus, the formation pattern of the second type products, 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones, in the arylglyoxals reaction with *N*-alkoxyureas has been clarified. It is necessary to use arylglyoxals with a strong electron-withdrawing substituent in 4-position of the aryl moiety to obtain these products. Additionally we have studied the interaction of 4-nitrophenylglyoxal with *N*-*n*-alkoxy-*N'*-phenylureas which have a long carbon chain in order to obtain 3-alkoxy-4,5-dihydroxy-5-(aryl)-1-phenylimida-zolidin-2-ones with lipophilic *N*-alkoxy moiety. The main reason for this was to find out whether the alkoxyl substituent in urea reagent influences the reaction or not.

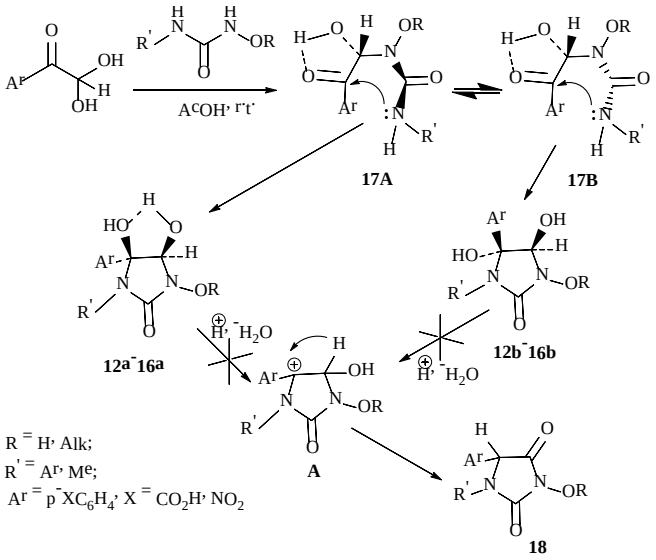


Scheme 8. The interaction of 4-nitrophenylglyoxal with *N*-alkoxy-*N'*-arylureas.

As the experimental results have shown, *N*-*n*-octyloxy-*N'*-phenylurea and *N*-*n*-dodecyloxy-*N'*-phenylurea interact with 4-nitrophenylglyoxal forming only a mixture of diastereomers of hydrophobic 3-alkoxy-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-ones **15,16** (Scheme 8).

The mixture of these diastereomers contains more than 90 % of *cis*-4,5-dihydroxy diastereomers **15a**,**16a**. The trace amounts of *trans*-4,5-dihydroxy diastereomers **15b**,**16b** can be easily removed by crystallization. The products of the 4-nitrophenylglyoxal interaction's with *N*-*n*-octyloxy-*N'*-phenylurea and *N*-*n*-dodecyloxy-*N'*-phenylurea demonstrate, that the nature of the *N*-alkoxy substituent in urea does not influence the reaction.

We propose the next scheme of the arylglyoxals interaction with *N*-hydroxyurea or *N*-alkoxyureas (Scheme 9) to explain the fact that diastereomers with *cis* orientation of 4-HO- and 5-HO-groups dominate over the *trans* 4,5-dihydroxy diastereomers in all the reactions which are reported in this study.



Scheme 9. The proposed mechanism of the interaction of *N*-alkoxy-*N'*-arylureas and *N*-alkoxy-*N'*-alkylureas with 4-carboxyphenylglyoxal and 4-nitrophenylglyoxal.

According to this scheme in the beginning of the interaction the open-chain *N*-substituted urea **17** is formed. Compounds **17** may be stabilized by the intramolecular hydrogen bond. The acyclic urea **17** form further the compounds **12**–**16**. Thus, the diastereomers **12a**-**16a** with 4-HO- and 5-HO-groups in the *cis*-conformation to each other have been produced. It is probable that the diastereomers **12a**-**16a** are also stabilized by the intramolecular hydrogen bond. *N*-Alkoxyurea **17A** slowly transforms into a conformation **17B** by the rotation of carbamoyl moiety around N–C bond or the *N*-alkoxy nitrogen inversion. The conformation **17B** eventually forms *trans*-4,5-dihydroxy diastereomers **12b**-**16b**.

Probably the low process temperature (approximately 20°C) preserves the further isomerization of the formed *cis*-4,5-dihydroxy diastereomers **12a**-**16a** into *trans*-4,5-dihydroxy diastereomers **12b**-**16b**.

It is evident that the presence of a strong electronegative substituent in the forth position of 5-aryl moiety, such as carboxyl group or nitro group, destabilizes "benzylic" cation **A** and makes the further transformation of the compounds **12-16** into hydantoins **18** impossible.

CONCLUSIONS

We have shown that reaction of 4-carboxyphenylglyoxal with *N*-alkoxy-*N*'-arylureas in acetic acid at room temperature produces only 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones. It is the new practical evidence of the possibility of obtaining only the second type products, 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones, from the interaction of arylglyoxals with *N*-hydroxyurea derivatives. Using *N*-propyloxy-*N*'-methylurea as a reagent in this reaction leads to the similar product – 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one. Obtaining 3-alkoxy-4,5-dihydroxy-5-arylimidazolidin-2-ones with lipophilicity fragment is also possible in this reaction. Thus, a new practical application of the interaction between arylglyoxals and *N*-alkoxyureas has been found.

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