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THE INTERACTION OF THE 4-CARBOXYPHENYLGLYOXAL WITH *N*-HYDROXYUREA AND *N*-ALKOXY-*N'*-ALKYL(ARYL)UREAS. THE STUCTURE OF 5-(4-CARBOXYPHENYL)-4,5-DIHYDROXY-1-METHYL-3-PROPYLOXYIMIDAZOLIDIN-2-ONE

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Abstract

Aim. The investigation of the reaction of 4-carboxyphenylglyoxal with *N*-hydroxyurea, different *N*-alkoxy-*N'*-arylureas and *N*-propyloxy-*N'*-methylurea in acetic acid medium and the product structure. Methods.^{1}H and ^{13}C NMR, mass spectra and XRD study. Results. 3-Alkoxy-4,5-dihydroxyimidazolidin-2-ones are the only products of *N*-alkoxy-*N'*-alkyl(aryl)ureas interaction with 4-carboxyphenylglyoxal. The possibility of obtaining such dominating products as 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones and 3-alkoxy-1-alkyl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones with *cis* orientation of 4-HO- and 5-HO-groups to each other has been proved in the experimental way. The product structure was revealed by the ^{1}H and ^{13}C NMR, mass spectra and XRD study. Also the structure of 5-(4-carboxyphenyl)-4*S*,5*S*-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one is discussed in this article. In this compound the endocyclic C(2)–C(3) bond is elongated to 1.562(2) Å) as compared to the average length of C(sp^3)–C(sp^3) ordinary bond. The N(1) atom has almost planar configuration whereas the N(2) atom has pyramidal configuration. The N(1)–C(1) bond is shorter than the N(2)–C(1) bond. 4-Carboxyphenylglyoxal reacts with *N*-hydroxyurea in acetic acid at room temperature with the selective formation of 5-(4-carboxyphenyl)-3-hydroxyimidazolidine-2,4-dione. Conclusions. 4-Carboxyphenylglyoxal reacts with *N*-propyloxy-*N'*-methylurea and *N*-alkoxy-*N*-arylureas in acetic acid at room temperature selectively producing 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one and 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones with *cis* orientation of 4-HO- and 5-HO-groups towards each other. In the same conditions 4-carboxyphenylglyoxal interacts with *N*-hydroxyurea yielding only 5-(4-carboxyphenyl)-3-hydroxyimidazolidine-2,4-dione.

Keywords: *3*-alkoxy-1,5-bis(aryl)-4,5-dihydroxyimidazolidin-2-ones; 3-alkoxy-1-alkyl-5-aryl-4,5-dihydroxyimidazolidin-2-ones; synthesis; structure.

ВЗАЄМОДІЯ 4-КАРБОКСИФЕНІЛГЛІОКСАЛЮ З *N*-ГІДРОКСИСЕЧОВИНОЮ ТА *N*-АЛКОКСИ-*N'*-АЛКІЛ(АРИЛ)СЕЧОВИНАМИ. БУДОВА 4,5-ДИГІДРОКСИ-5(4-КАРБОКСИФЕНІЛ)-1-МЕТИЛ-3-ПРОПІЛОКСИІМІДАЗОЛІДИН-2-ОНУ

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Анотація

Мета. Дослідження взаємодії 4-карбоксифенілгліоксалю з *N*-гідроксисечовиною, різними *N*-алкокси-*N'*-арилсечовинами і *N*-пропілокси-*N'*-метилсечовиною в оцтовій кислоті та встановлення структури продуктів. Метод. Спектроскопія ЯМР ^{1}H і ^{13}C, мас-спектрометрія та метод рентгеноструктурної дифракції. Результати.

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Знайдено, що 3-алкокси-4,5-дигідроксиімідазолідин-2-они є єдиними продуктами взаємодії *N*-алкокси-*N'*-арилсечовин і *N*-алкокси-*N'*-алкілсечовин з 4-карбоксифенілгліоксалем у оцтовій кислоті за кімнатної температури. Головними і переважними продуктами реакції є такі діастереомери 3-алкокси-4,5-дигідроксиімідазолідин-2-онів, які мають *цис*-орієнтацію 4-НО- і 5-НО-груп відповідно одна іншій. Діастереомери з *транс*-орієнтацією 4-НО- і 5-НО-груп відповідно одна іншій утворюються у вельми незначної кількості. Будову продуктів доведено в сукупності за допомогою спектрів ^{1}H і ^{13}C ЯМР, масспектрів, а також методом рентгеноструктурної дифракції досліджено будову 4*S*,5*S*-дигідрокси-5-(4-карбоксифеніл)-1-метил-3-пропілоксиімідазолідин-2-ону. Наводиться обговорення її особливостей. Встановлено, що в молекулі 4*S*,5*S*-дигідрокси-5-(4-карбоксифеніл)-1-метил-3-пропілоксиімідазолідин-2-ону ендоциклічний зв'язок C(2)–C(3) подовжений до 1.562(2) Å порівняно із середньою величиною 1.540 Å для одинарного зв'язку C(sp^3)–C(sp^3). Атом Нітрогену N(1) має майже планарну конфігурацію, сума валентних кутів складає 354.4(1)°. Атом Нітрогену N(2) має пірамідальну конфігурацію, сума валентних кутів складає 335.2(1)°). Зв'язок N(1)–C(1) коротший (1.357(2) Å), ніж зв'язок N(2)–C(1) (1.393(2) Å). У тих же умовах 4-карбоксифенілгліоксаль реагує з *N*-гідроксисечовиною з селективним утворенням 3-гідрокси-5-(4-карбоксифеніл)імідазолідин-2,4-діону.

Ключові слова: 3-алкокси-1,5-бис(арил)-4,5-дигідроксиімідазолідін-2-они; 3-алкокси-1-алкіл-5-арил-4,5-дигідроксиімідазолідін-2-они; синтез; будова.

ВЗАИМОДЕЙСТВИЕ 4-КАРБОКСИФЕНИЛГЛИОКСАЛЯ С *N*-ГИДРОКСИМОЧЕВИНОЙ И *N*-АЛКОКСИ-*N'*-АЛКИЛ(АРИЛ)МОЧЕВИНАМИ. СТРОЕНИЕ 4,5-ДИГИДРОКСИ-5(4-КАРБОКСИФЕНИЛ)-1-МЕТИЛ-3-ПРОПИЛОКСИИМИДАЗОЛИДИН-2-ОНА

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Аннотация

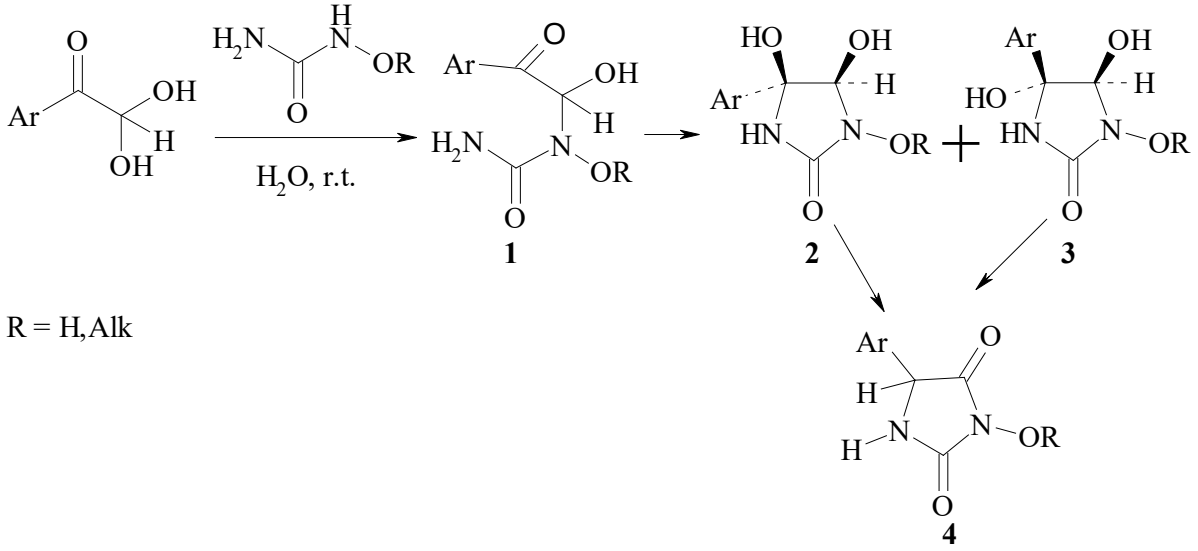
Цель. Исследование взаимодействия 4-карбоксифенилглиоксаля с *N*-гидроксимочевиной, различными *N*-алкокси-*N'*-арилмочевинами и *N*-пропилокси-*N'*-метилмочевиною в уксусной кислоте и установление структуры продуктов. Метод. Спектроскопия ЯМР ^{1}H и ^{13}C, масс-спектрометрия и метод рентгенноструктурной диффракции. Результаты. Найдено, что единственными продуктами взаимодействия *N*-алкокси-*N'*-арилмочевин и *N*-алкокси-*N'*-алкилмочевин с 4-карбоксифенилглиоксалем в уксусной кислоте при комнатной температуре являються 3-алкокси-4,5-дигидроксиимидазолидин-2-оны. Главными и преимущественными продуктами реакции являются диастереомеры 3-алкокси-4,5-дигидроксиимидазолидин-2-онов, имеющие *цис*-ориентацию 4-НО- и 5-НО-групп относительно друг друга. Диастереомеры с *транс*-орієнтацией 4-НО- и 5-НО-групп относительно друг друга образуются в следовых количествах. Структуру продуктов реакции доказано с помощью спектров ЯМР ^{1}H и ^{13}C ЯМР, масс-спектров, а также методом рентгеноструктурной дифракции исследовано строение 4*S*,5*S*-дигидрокси-5-(4-карбоксифенил)-1-метил-3-пропилоксиимидазолидин-2-она. Приводится обсуждение её особенностей. Найдено, что в молекуле 4*S*,5*S*-дигидрокси-5-(4-карбоксифенил)-1-метил-3-пропилоксиимидазолидин-2-она эндоциклическая связь C(2)–C(3) удлиненна до 1.562(2) Å по сравнению с средней величиной 1.540 Å для одинарной связи C(sp^3)–C(sp^3). Атом азота N(1) имеет почти плоскую конфигурацию, сумма валентных углов составляет 354.4(1)°. Атом азота N(2) имеет пирамидальную конфигурацию, сумма валентных углов составляет 335.2(1)°). Связь N(1)–C(1) короче (1.357(2) Å), чем связь N(2)–C(1) (1.393(2) Å). В тех же условиях 4-карбоксифенилглиоксаль реагует с *N*-гидроксимочевиною с селективным образованием 3-гидрокси-5-(4-карбоксифенил)имидазолидин-2,4-диона.

Ключевые слова: 3-алкокси-1,5-бис(арил)-4,5-дигидроксиимидазолидин-2-оны; 3-алкокси-1-алкил-5-арил-4,5-дигидроксиимидазолидин-2-оны; синтез; строение.

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 proved 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 or 3-alkoxy-4,5-dihydroxy-5-arylimidazolidin-2-ones 2,3 respectively and 3-hydroxy- or 3-alkoxyhydantoins 4 respectively.



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

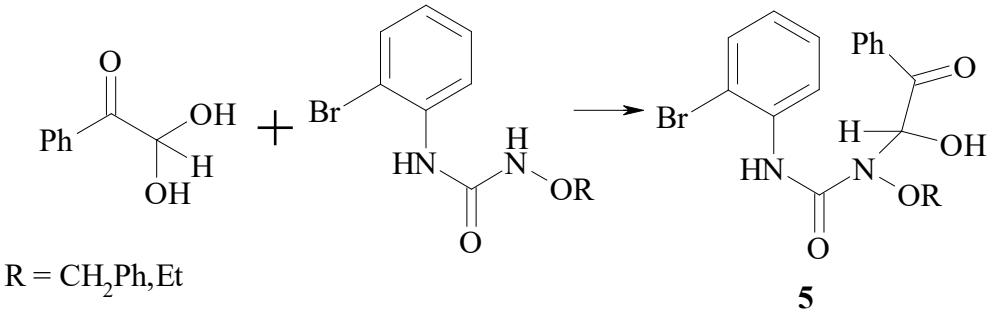
The mechanism of this interaction cannot be completely proved because of the lack of experimental evidence. In any case the formation pattern of each product type is valuable. It is important to know this pattern not only in order to determine the reaction mechanism, but also to get further perspective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

The relevance of the products which can be obtained by the arylglyoxals interaction with *N*-hydroxyurea or *N*-alkoxyureas is significant because of the importance of imidazolidin-2-ones and imidazolidine-2,4-diones among the nitrogen containing heterocycles [7–21]. Arylglyoxals are widely used in synthesis of these biologically active nitrogen containing heterocycles [22; 23], too.

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 interaction product strongly depends on the glyoxal's reagent.

However, when we use arylglyoxals with electron-donating groups in aryl moiety the substituted ureas 1 might not be the only products of this reaction [1]. As usual the first type products, substituted ureas 1, forms imidazolidin-2-ones 2,3, which further transformation into hydantoins 4.

Nevertheless, it is possible to obtain only the substituted ureas 5 in this interaction. For this result the strong intramolecular effects should take place in the compounds 5 [2; 6] (Scheme 2).



Scheme 2. The substituted ureas' formation as the only product in the interaction of arylglyoxals with *N*-alkoxyureas [2, 6]

The second type products mixture of 4,5-dihydroxyimidazolidin-2-ones 2,3, and the third type products, hydantoins 4, are obtained in all the other cases. This fact serves as a clear evidence that the substituted ureas 1 cyclization into 5-arylimidazolidin-2-ones 2 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 2,3, turn into the third type products, hydantoins 4 [1; 6], but not always.

For now, the most convenient method of getting the third type product only is to use acetic acid as a solvent for the reaction of arylglyoxals with *N*-hydroxyurea or *N*-alkoxyureas. The

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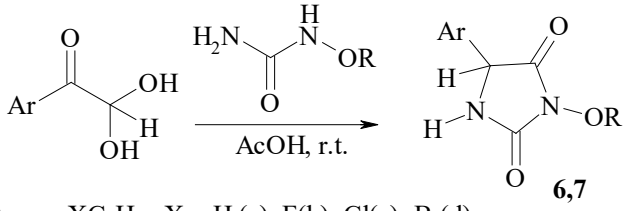
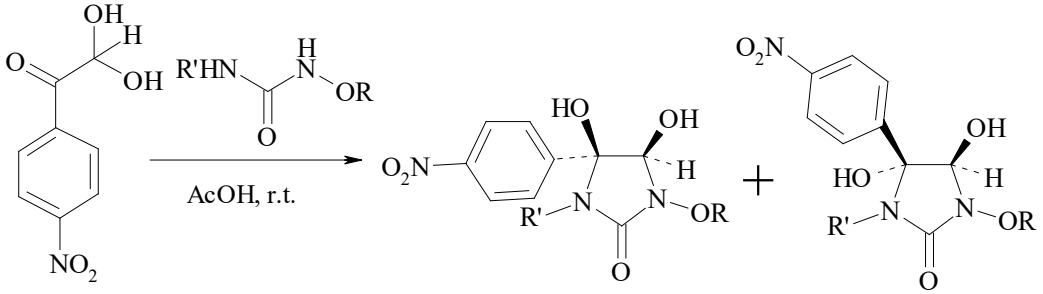
products are only 3-hydroxyhydantoines 6 or 3-alkoxyhydantoines 7 respectively [3] (Scheme 3).



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 arylglyoxals interaction with *N*-hydroxyurea or *N*-alkoxyureas in acetic acid [3]

Only the second type products were fixed 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). 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)imidazoleidin-2-ones **9a** [5] (Scheme 4). These compounds have 4-hydroxyl and 5-hydroxyl groups in the *cis*-conformation to each other.



R=R'=H (**8**)
R=Alk, R'=Ar (**9**)
R=R'=Alk (**10**)

Scheme 4. The products of 4-nitrophenylgyoxal interaction with *N*-hydroxyurea [4] and *N*-alkoxy-*N'*-alkyl(aryl-)ureas [5]

It has been 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 **10a** (**10a** : **10b**=99 : 1) [5] (Scheme 4).

The diastereomers of 5-aryl-4,5-dihydroxyimidazolidin-2-one **8a,9a,10a** with *cis* orientation of 4-HO- and 5-HO-groups to each other prevailed over the *trans* isomers in all the experiments**.**

To sum up all the information about arylglyoxals interaction with *N*-hydroxyurea derivatives we should note that the experimental investigation of the second type products **2,3** formation overall pattern needs to be continued. For this reason, we have chosen to explore the reaction of 4-carboxyphenylglyoxal with the *N*-hydroxyurea, the 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) and VARIAN VNMRS 400 spectrometer (100 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-Carboxyphenylglyoxal hydrate was obtained according to the standard procedure by 4-acetylbenzoic acid oxidation by SeO_2, pink powder, unstable. ^{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).

5-(4-Carboxyphenyl)-3-hydroxyimidazolidine-2,4-dione (11). The solution of *N*-hydroxyurea (74 mg, 0.970 mmol) in acetic acid (8 mL) was added to the mixture of 4-carboxyphenylglyoxal hydrate (166 mg, 0.845 mmol) and acetic acid (10 mL) at stirring. The reaction mixture was stirred during 23 h at 20°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 (7 mL) and dried under vacuum (4 mmHg), giving 145 mg (67 %) of 5-(4-carboxyphenyl)-3-hydroxyimidazolidine-2,4-dione monohydrate **11**, white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.360(1H, s, CH); 7.468 (2H, d, ^3J = 8.0 Hz, C(2)H, C(6)H Ar); 7.984 (2H, d, ^3J = 8.0 Hz, C(3)H, C(5)H Ar); 8.799 (1H, s, NH); 10.632 (1H, s, NOH); 13.062 (1H, s, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 57.34 (CH); 126.99 C(2)H, C(6)H Ar; 129.69 C(3)H, C(5)H Ar; 130.93 C(1) Ar; 140.00 C(4) Ar; 154.28 [N(C=O)N]; 166.89 COOH; 167.19 C=O. MS (FAB) m/z 237 $[M+H]^+$ (87); 88 (100). Anal. Calc. for $C_{10}H_8N_2O_5 \bullet H_2O$, %: C 47.24; H 3.96; N 11.02. Found, %: C 47.01; H 4.06; N 10.97.

The aqueous filtrate was evaporated under vacuum (4 mmHg) at 20°C, the residue was extracted by ethyl acetate (8 mL), the extract was evaporated under vacuum additionally yielding 41 mg (19 %) compound **11**.

N-n-Butyloxy-N'-phenylurea. The solution of phenylisocyanate (1.240g, 10.413 mmol) in benzene (5 mL) was added to the solution of *n*-butyloxyamine (0.975 g, 10.933 mmol) in benzene (8 mL), the reaction mixture was kept at 60ºC during 30 min, then the solvent was evaporated under vacuum (20 mmHg), hexane (8 mL) was added. After keeping at -5ºC during 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, mp. 77–79 ºC. ^{1}H NMR (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 7.15.

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 during 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, mp. 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_6H_4); 7.855 (2H, d, ^3J = 8.4 Hz, C(3)H, C(5)H C_6H_4); 12.977 (1H, s, COOH). ^{1}H NMR (300 MHz, CD_3CN): 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_6H_4); 7.914 (2H, d, ^3J = 8.4 Hz, C(3)H, C(5)H C_6H_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 $[M+H-H_2O]^+$ (9); 250 (26); 209 (100); 149 (49). Anal. Calc. for $C_{20}H_{22}N_2O_6 \bullet H_2O$, %: C 59.40; H 5.98; N 6.93. Found, %: C 59.07; H 6.13; N 6.85.

4,5-Dihydroxy-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 during 38 h at 20°C, then the negligible precipitate was filtered off, 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}H NMR spectrum). This mixture was extracted by water (4 mL) at 4°C during 23 h, then the obtained precipitate was filtered off, 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_6H_4Me); 7.017–7.076 (2H, m, CHOH and OH); 7.241 (2H, d, ^3J = 8.7 Hz, C(2)H, C(6)H C_6H_4Me); 7.577 (2H, d, ^3J = 8.1 Hz, C(2)H, C(6)H C_6H_4COOH); 7.842 (2H, d, ^3J = 8.1 Hz, C(3)H, C(5)H C_6H_4COOH); 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_6H_4Me; C–N]; 156.92 (NC(=O)N); 166.90 (COOH). MS (FAB) m/z 359 $[M+H]^+$ (41); 341 $[M+H-H_2O]^+$ (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_2O, %: C 57.44; H 5.35; N 7.44. Found, %: 55.78; H 5.54; N 7.42.

*5-(4-Carboxyphenyl)-4S,5S-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one (14)***.** 4-Carboxyphenylglyoxal hydrate (74.6 mg, 0.380 mmol) was added to the solution of *N*-propyloxy-*N'*-methylurea [5] (55.7 mg, 0.421 mmol) in acetic acid (5 mL), the reaction mixture was stirred during 26 h at 22°C, then the negligible precipitate was filtered off, 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_2O (2 mL), dried under vacuum (2 mmHg), yielding 104 mg (84 %) of monohydrate of 5-(4-carboxyphenyl)-4*S*,5*S*-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one **14**, colorless crystals, mp. 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_6H_4COOH); 7.970 (2H, d, ^3J = 8.7 Hz, C(3)H, C(5)H C_6H_4COOH); 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_6H_4]; 130.75 [C(4) C_6H_4]; 144.62 [C(1) C_6H_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.

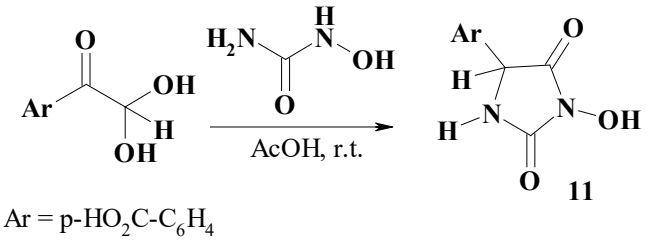
The crystals of compound **14** were grown from ethanol, EtOH, triclinic, $C_{14}H_{18}N_2O_6$•C_2H_6O, M = 356.37, space group *P-1* , *a* = 8.1633(3), *b* = 10.5552(4), *c* = 11.6150(4)Å, *α* = 76.899(2), *β* = 84.240(2), *γ* = 70.272(2)°, V = 917.24(6)Å^3, Z = 2, d_c = 1.290, μ 0.102 мм$^{-1}$, F(000) 380, crystal size ca. 0.21 × 0.31 × 0.39 mm. All crystallographic measurements were performed at 173K on a Bruker Smart Apex II diffractometer operating in the ω scans mode. The intensity data were collected for reflections within $\theta_{max} \leq 26.5°$ using Mo-K_α radiation (λ = 0.71078 Å). The intensities of 16552 reflections were collected (3787 unique reflections, R_{merg} = 0.0306). The structure was solved by with direct methods and refined with the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package [24]. The solvate ethanol molecule is disordered in two positions A and B with occupancies 0.36 and 0.64 respectively. All the CH hydrogen atoms were placed at calculated positions and refined as 'riding' model. The hydrogen atoms that supported hydroxyl and carboxylate groups were found in DF synthesis and refined isotropically. The convergence was obtained at R1 = 0.0452 and wR2 = 0.1143 for 2907 observing reflections with $I \geq 2\sigma(I)$, R1 = 0.0616 and wR2 = 0.1236, GOF = 1.047 for 3787 independent reflections, 265 parameters, 8 restraints, the largest and minimal peaks in the final difference map 0.29 and – 0.20 e/Å^3.

The atomic coordinates, molecular geometry parameters, and crystallographic data of compound **14** 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 2064374.

Results and discussion

We have found that *N*-hydroxyurea reacts with 4-carboxyphenylglyoxal in acetic acid medium at room temperature yielding only 5-(4-carboxyphenyl)-3-hydroxyimidazolidine-2,4-dione **11** (Scheme 5).

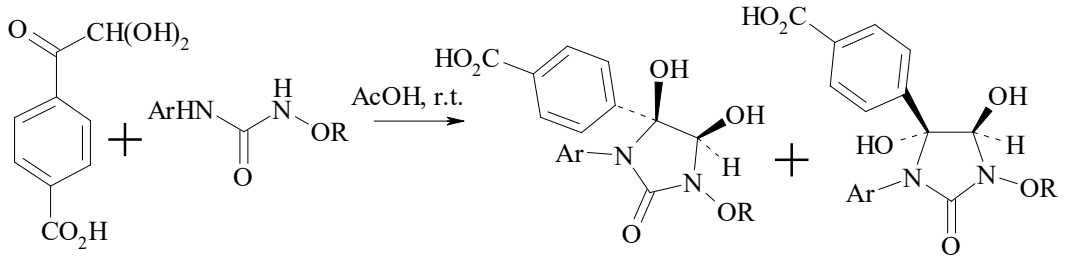
The *N*-hydroxyhydantoin 11 structure was revealed by the ^{1}H and ^{13}C NMR, and mass spectrum. In the same manner the other arylglyoxals react with *N*-hydroxyurea [3].



Ar = p-HO_2C-C_6H_4

Scheme 5. The interaction of 4-carboxyphenylglyoxal with N-hydroxyurea

We have 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-dihydroxyimidazolidin-2-ones 12, 13 (Scheme 6).

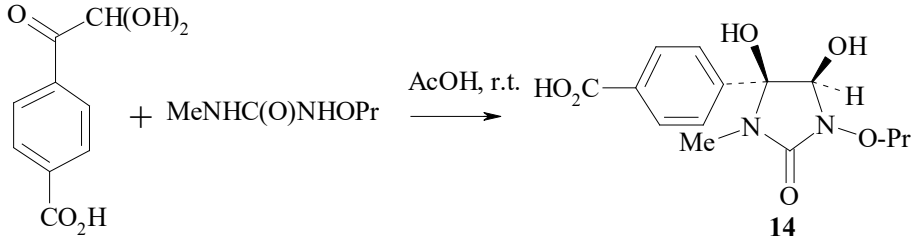


Ar=Ph, R=Bu(**12**)
Ar = p-MeC_6H_4, R=Me(**13**)

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

We assume, that likewise 4-nitrophenylgyoxal's interaction with *N*-alkoxy-*N'*-arylureas [5], that the main product in both cases is similar. In this 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%. The *trans* diastereomers 12b,13b have been observed in reaction products in the trace amount as well. Firstly, the *cis* orientation of 4-HO- and 5-HO-groupe has been proposed for the compounds 12a,13a based on their ^{1}H NMR spectra. For the compounds 12a,13a the doublet of CHOH proton is situated in the higher field [4.856 ppm (12a); 4.891 ppm (13a)], then the doublet of CHOH proton of *trans* diastereomers [5.132 ppm (12b); 5.154 ppm (13b)]. Earlier it has been demonstrated for 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones 8a and 8b [4], 3-alkoxy-1-aryl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones 9,10 [5].

In a similar way the *N*-propyloxy-*N*'-methylurea's interaction with 4-carboxyphenylglyoxal produces only 5-(4-carboxyphenyl)-4*S*,5*S*-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one 14 (Scheme 7).



Scheme 7. 4-Carboxyphenylglyoxal's interaction with *N*-propyloxy-*N*'-methylurea

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].

The structure of 5-(4-carboxyphenyl)-4*S*,5*S*-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one 14 has been proved by XRD study (Figures 1, 2, Table 1).

In the molecule of compound 14 the imidazolidinone cycle is non planar and has envelope conformation. Thus, the C(1), C(2), N(1), and N(2) atoms occupy position at the same plane with rms deviation of the fitted atoms 0.0274 Å. The C(2), C(3), and N(2) atoms plane makes with previous plane the dihedral angle which is equal to 35.1(1).

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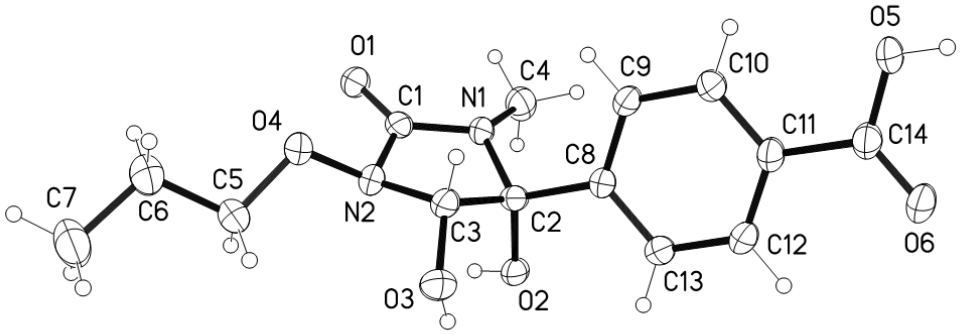

Fig. 1. Molecular structure of 5-(4-carboxyphenyl)-4*S*,5*S*-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one 14 with atoms represented by thermal vibration ellipsoids at 50 % probability level

The C(2)–O(2)H and C(3)–O(3)H hydroxyl groups are *cis*-oriented to each other (the O(2)–C(2)–C(3)–O(3) torsion angle is 38.68(17)°).

The N(1) atom has almost planar configuration (the sum of bond angles (Σβ) is 354.4(1)°) whereas the N(2) atom has pyramidal configuration (Σβ is equal 335.2(1)°).

The N(1)–C(1) bond is shorter (1.357(2) Å) than N(2)–C(1) bond (1.393(2) Å). This length difference indicates the stronger conjugation between lone pair of the N(1) atom and the C(1)=O(1) carbonyl compared to conjugation between the lone pair of N(2) atom and the C(1)=O(1) carbonyl bond.

The endocyclic C(2)–C(3) bond (the length is 1.562(2) Å) in the molecule 14 is elongated as compared to the average length of C(sp^3)–C(sp^3) ordinary bond (1.540 Å [25]) . This phenomenon has been observed in the polycyclic 3-hydroxy- and 3-alkoxyimidazolidin-2-ones [26], as well. And vice versa, the exocyclic C(5)–C(6) bond (1.491(2) Å) and C(6)–C(7) bond (1.519(3)Å) is shortened to the average length of C(sp^3)–C(sp^3) ordinary bond. This phenomenon has been observed in 3-ethoxy-5-phenylimidazolidine-2,4-dione [3].

In the crystal the molecules of the compound 14 are linked by the four O-H···O hydrogen bonds (Figure 2, Table 1).

Table 1

The hydrogen bonds in the crystal of compound 14

D-H···A (symmetry operation)	d(D-H), Å	d(D···A), Å	angle(DHA), °
O2-H(2O)···O7 (*1 x, y, z+1*)	0.855(9)	2.6180(16)	175(2)
O3-H(3O)···O2 (*1-x, 1-y, 2-z*)	0.845(10)	2.8118(16)	145(2)
O5-H(5O)···O1 (*x, y, z-1*)	0.842(9)	2.6588(15)	167(2)
O7-H(7O)···O6	0.845(10)	2.7307(18)	171(2)

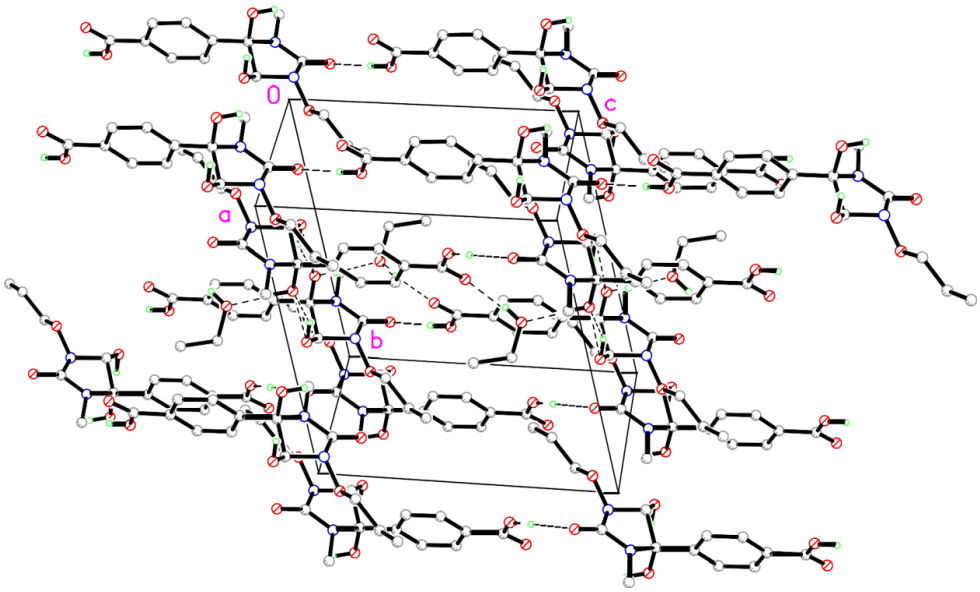

Fig. 2. Molecular packing of compound 14 in the crystal

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 aryl's moiety to obtain these products.

Conclusions

We have proved that 4-carboxyphenylglyoxal reaction 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. Using *N*-propyloxy-*N*'-methylurea as a urea's reagent in this reaction leads to 5-(4-carboxyphenyl)-4*S*,5*S*-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one. The structure of 5-(4-carboxyphenyl)-4*S*,5*S*-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one 14 has been proved by the XRD study. It means that 4-carboxyphenylglyoxal reacts with *N*-propyloxy-*N*'-methylurea and *N*-alkoxy-*N*-arylureas in acetic acid at room temperature selectively producing 5-(4-carboxyphenyl)-4*S*,5*S*-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one 14 and 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4*S*,5*S*-dihydroxyimidazolidin-2-ones 12a,13a. In these compounds the hydroxyl groups are *cis*-oriented towards each other. We have found that 4-carboxyphenylglyoxal reaction with *N*-hydroxyurea in acetic acid at room temperature produces only the 5-(4-carboxyphenyl)-3-hydroxyimidazolidine-2,4-dione 11

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