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Synthesis and crystal structure of new imidazolidine-2,4-dione and imidazolidin-2-one derivatives

Vasiliy G. Shtamburg,[a] Andrey A. Anishchenko,[a] Victor V. Shtamburg,[b] Oleg V. Shishkin,[b] Roman I. Zubatyuk,[b] Alexander V. Mazepa,[c] Ildar M. Rakipov[c] and Remir G. Kostyanovsky*[d]

[a] *Department of Chemistry, Dnepropetrovsk National University, 49050 Dnepropetrovsk, Ukraine*
[b] *STC Institute for Single Crystals, National Academy of Sciences of Ukraine, 61001 Kharkov, Ukraine*
[c] *A. V. Bogatsky Physico-Chemical Institute, National Academy of Sciences of Ukraine, 65080 Odessa, Ukraine*
[d] *N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 495 137 8284; e-mail: kost@center.chph.ras.ru*

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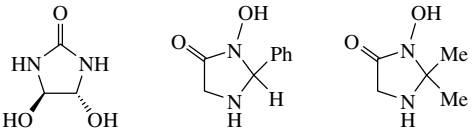
Arylglyoxals condense with *N*-hydroxyurea in water *via* intermediate formation of *N*-hydroxy-*N*-[hydroxy(aroyl)]methylureas and 3,4,5-trihydroxy-5-arylimidazolidin-2-ones to yield 3-hydroxy-5-aryl-imidazolidine-2,4-diones as end products; the 3,4,5-trihydroxy-5-(*p*-chlorophenyl)imidazolidin-2-one and 3-hydroxy-5-phenylimidazolidine-2,4-dione crystallise as racemates.

Imidazolidin-2-one **A**, its derivatives, glicolurils and imidazolidin-4-one **B** form homochiral crystals (conglomerates), and compounds **A** and **B** undergo spontaneous resolution.[1(a)–(d)] However, imidazolidin-4-one **C**, which crystallises in the same space group, affords an unresolvable conglomerate because its conformation chirality is held only in a crystal.[1(c)]



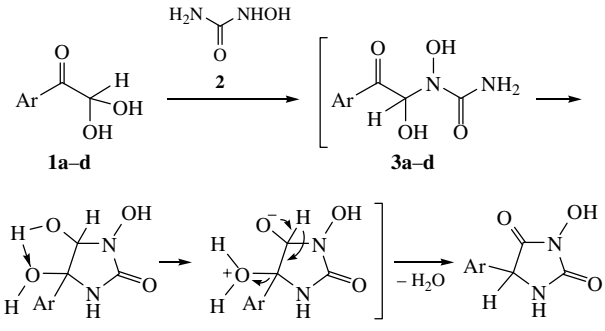
A **B** **C**

With the aim of seeking conglomerates, this study was devoted to the synthesis of new imidazolidin-2-ones and hydantoins, which are structurally similar to compounds **A**–**C**.

In the presence of acids α-dicarbonyl compounds react with 1,3-disubstituted ureas to form derivatives of 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones.[2] In the presence of KOH, phenylglyoxal condenses with methylurea with the formation of 1-methyl-5-phenylhydantoin,[3] the condensation with *N*,*N*′-dimethylurea yields 1,3-dimethyl-5-phenylhydantoin.[4]

We found that phenylglyoxal **1a** condensed with freshly obtained *N*-hydroxyurea **2** in neutral aqueous media probably *via* intermediates **3a** and **4a** yielding 3-hydroxy-5-phenylhydantoin **5a**† as the end product (Scheme 1). Other arylgyoxals **1b–d** react in the same manner to yield hydantoins **5b–d**; intermediates **3b** and **4c** can be isolated. Probably, at the first stage, arylglyoxal attacks *N*-hydroxyurea **2** at the more nucleophilic nitrogen atom connected with the hydroxy group. In accordance with this scheme, for *p*-tolylglyoxal **1b**, the product of the first stage (urea **3b**) was isolated along with the end product, 3-hydroxy-5-*p*-tolylhydantoin **5b**.

At the second stage, ureas **3** cyclise to 3,4,5-trihydroxy-5-arylimidazolidin-2-ones **4**. Thus, if *p*-chlorophenylglyoxal **1c** condensed with *N*-hydroxyurea **2** under mild conditions (20 °C), imidazolidinone **4c** was isolated. At the next stage, the intramolecular hydrogen bonding H(4′)···O(5) is supposed to take place in intermediate **4** yielding zwitterion **4′**. Probably, the orbital interaction $n_{O(4)} \rightarrow \sigma^*_{C(4)–H}$ causes the electron density transfer to the orbital $\sigma^*_{C(4)–H}$ in the intermediate **4′**. The atom H(4) becomes a quasi-nucleophile. On the other hand, H_2O is a good leaving group. These factors are responsible for the H(4) migration to the C(5) atom with H_2O group nucleophilic substitution. The **4** → **5** rearrangement may be regarded as a synchronous process, and it is a route to the formation of known imidazolidine-2,4-diones, namely, 3-hydroxy-5-arylhydantoins **5**. The rearrangement of the disodium salt of phenylmalonohydroxamic acid with toluenesulfonyl chloride led to the formation of 3-*p*-tosyloxy-5-phenylhydantoin.[5]



1a–d **3a–d** **4a–d** **4′a–d** **5a–d**

a Ar = Ph
b Ar = *p*-Tol
c Ar = *p*-ClC_6H_4
d Ar = C_4H_3S

Scheme 1

The structures of compounds **4c** and **5a** were established by X-ray analysis‡ (Figures 1 and 2). In **4c** the five-membered ring adopts envelope conformation [the C(2) atom lies 0.478(2) Å off the plane of remaining ring atoms]. Atom N(2) has higher pyramidal configuration than atom N(1), the sum of bond angles centered at the N(2) atom ($\sum\beta$) is 337.6° [for N(1) $\sum\beta$ = 354.8°]. In the case of **5a**, the heterocycle is almost planar (RMS deviation of atoms is 0.013 Å). The N(2) atom has almost perfectly planar configuration ($\sum\beta$ = 359.7°), probably, due to conjugation with adjacent carbonyl groups. As a result, the N(2)–O(2) bond is shorter [1.3745(17) Å in **5a** compared to 1.4047(14) Å in **4c**]. However, note that the N(2)–C(1) bond [1.404(2) Å] in **5a** is even longer than that in **4c**. At the same time, the N(2)–C(2) bond length [1.337(2) Å] is typical of amide fragments.[6] Therefore, the elongation of the N(2)–C(1) bond in **5a** can be explained by

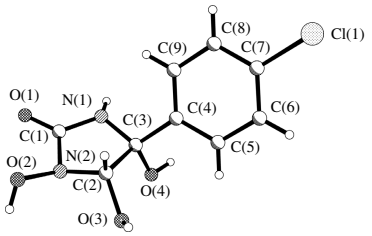


Figure 1 Molecular structure of **4c**. Selected bond lengths (Å) and bond angles (°): Cl(1)–C(7) 1.7402(13), O(1)–C(1) 1.2300(15), O(2)–N(2) 1.4047(14), O(3)–C(2) 1.3874(14), O(4)–C(3) 1.4203(14), N(1)–C(1) 1.3462(16), N(1)–C(3) 1.4516(15), N(2)–C(1) 1.3822(16), N(2)–C(2) 1.4524(16), C(2)–C(3) 1.5587(17), C(3)–C(4) 1.5116(17); O(1)–C(1)–N(1) 126.60(11), O(1)–C(1)–N(2) 125.26(11), O(2)–N(2)–C(2) 115.14(10), O(2)–N(2)–C(1) 113.74(10), C(1)–N(2)–C(2) 108.70(10), C(1)–N(1)–C(3) 112.26(10), O(3)–C(2)–N(2) 111.54(10), O(3)–C(2)–C(3) 112.95(11), O(4)–C(3)–C(4) 109.77(10), N(1)–C(3)–C(2) 100.17(9), N(2)–C(2)–C(3) 101.14(9).

† N-*Hydroxy*-N-*[hydroxy(*p-*methylbenzoyl)]methylurea* **3b**. A solution of freshly obtained *N*-hydroxyurea **2** (0.359 g, 4.718 mmol) in H_2O (5 ml) was added to a warm (45–50 °C) solution of *p*-tolylglyoxal **1b** hydrate (0.784 g, 4.718 mmol) in water (25 ml). The reaction mixture was stirred at 20 °C for 60 h; then, it was kept for 24 h. The precipitate was filtered off and washed with water (4 ml) to yield 0.345 g (32.6%) of **3b**, colourless solid, mp 134–136 °C (decomp.). ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ: 2.38 (s, 3H, Me), 5.95 (d, 1H, C*H*OH, ^3J 7.5 Hz), 6.49 (d, 1H, CHO*H*, ^3J 7.5 Hz), 6.51 (br. s, 2H, NH_2), 7.31 [d, 2H, C(3)H, C(5)H, ^3J 7.8 Hz], 7.88 [d, 2H, C(2)H, C(6)H, ^3J 7.8 Hz], 9.28 (s, 1H, NOH). IR (ν/cm^{-1}): 3415 (OH), 3340, 3280 (NH_2), 1685 (C=O), 1645 (C=O). MS [FAB, H$^+$, *m/z*, I_{rel} (%)]: 225 [M + H]$^+$ (41.8), 207 (16.4), 164 (97.5), 119 (100). Found (%): N, 12.20. Calc. for $C_{10}H_{12}N_2O_4$ (%): N, 12.49. The water filtrate was concentrated *in vacuo* (2 Torr), the formed precipitate was filtered off to yield 0.490 g (46.3%) of *3-hydroxy-5-(*p-*tolyl)hydantoin* **5b** monohydrate, colourless crystals, mp 136–139 °C (decomp.). ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ: 2.32 (s, 3H, Me), 5.18 (s, 1H, CH), 7.21 [d, 2H, C(3)H, C(5)H, ^3J 9.3 Hz], 7.24 [d, 2H, C(2)H, C(6)H, ^3J 9.3 Hz], 8.69 (s, 1H, NH), 10.56 (br. s, 1H, OH). IR (ν/cm^{-1}): 3570 (OH), 3270 (NH), 1770 (C=O), 1720 (C=O). MS [FAB, H$^+$, *m/z*, I_{rel} (%)]: 207 [M + H]$^+$ (100). Found (%): C, 53.65; H, 5.51; N, 12.38. Calc. for $C_{10}H_{10}N_2O_3{\cdot}H_2O$ (%): C, 53.67; H, 5.39; N, 12.49.

*3,4,5-Trihydroxy-5-(*p-*chlorophenyl)imidazolidin-2-one* **4c**. To a solution of freshly obtained *N*-hydroxyurea **2** (0.230 g, 3.00 mmol) in water (15 ml) the hydrate of *p*-chlorophenylglyoxal **1c** (0.560 g, 3.00 mmol) was added, the mixture was vigorously stirred at 20 °C for 24 h, kept for 14 days; then, negligible precipitate was filtered off and the filtrate was concentrated *in vacuo* (1 Torr). The precipitated solid was filtered off yielding 0.501 g (59.5%) of **4c** dihydrate, colourless crystals, mp 103–106 °C (THF–C_6H_{14}). ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ: 4.52 (d, 1H, C*H*OH, ^3J 7.2 Hz), 6.23 (s, 1H, OH), 6.48 (d, 1H, CHO*H*, ^3J 7.2 Hz), 7.49 [d, 2H, C(2)H, C(6)H, ^3J 8.4 Hz], 7.52 [d, 2H, C(3)H, C(5)H, ^3J 8.4 Hz], 8.10 (br. s, 1H, NH), 9.07 (s, 1H, NOH). IR (ν/cm^{-1}): 3605 (OH), 3475 (OH), 3240 (NH), 1720 (C=O). MS [FAB, H$^+$, *m/z*, I_{rel} (%)]: 247 [M + H]$^+$ (32.3), 245 [M + H]$^+$ (100), 229 (17.2), 227 (51.5). Found (%): N, 9.82. Calc. for $C_9H_9ClN_2O_4{\cdot}2H_2O$ (%): N, 9.98.

3-Hydroxy-5-phenylimidazolidine-2,4-dione **5a**. A solution of freshly obtained *N*-hydroxyurea **2** (0.190 g, 2.5 mmol) in H_2O (5 ml) was added to a warm (40–45 °C) solution of the hydrate of phenylglyoxal **1a** (0.381 g, 2.5 mmol) in water (5 ml). The reaction mixture was stirred at 18 °C for 2 h; then, it was kept for 22 h. Water was removed *in vacuo* (2 Torr), the residue was twice extracted by Et_2O (15 ml). The precipitated crystals were filtered off and dried *in vacuo*, yielding 0.408 g (77%) of the monohydrate of **5a**, colourless crystals, after second crystallization (THF–C_6H_{14}) mp 175–176 °C (decomp.). ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ: 5.24 (s, 1H, PhC*H*), 7.30–7.50 (m, 5H, Ph), 8.74 (s, 1H, NH), 10.60 (br. s, 1H, NOH). IR (ν/cm^{-1}): 3570 (OH), 3280 (NH), 1770 (C=O), 1720 (C=O). MS [EI, *m/z*, I_{rel} (%)]: 193 [M + H]$^+$ (0.7), 192 [M]$^+$ (4.0), 176 (40.3), 175 (7.7), 174 (14.7), 164 (8.2), 147 (9.0), 133 (14.5), 132 (11.1), 119 (6.8), 106 (11.4), 105 (86.8), 104 (100), 103 (77.9), 91 (9.2), 78 (27.3), 77 (67.2), 70 (18.0), 59 (20.0). MS [FAB, Na$^+$, *m/z*, I_{rel} (%)]: 215 [M + Na]$^+$ (54.3), 193 [M + H]$^+$ (100), 176 (33.7). Found (%): C, 51.77; H, 4.61; N, 13.55. Calc. for $C_9H_8N_2O_3{\cdot}H_2O$ (%): C, 51.43; H, 4.80; N, 13.33.

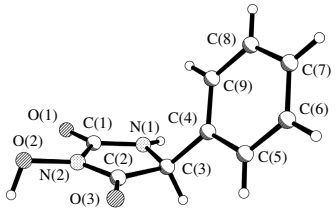


Figure 2 Molecular structure of **5a**. Selected bond lengths (Å) and bond angles (°): O(3)–C(2) 1.211(2), O(2)–N(2) 1.3745(17), O(1)–C(1) 1.201(2), N(2)–C(2) 1.337(2), N(2)–C(1) 1.404(2), N(1)–C(1) 1.332(2), N(1)–C(3) 1.447(2); C(2)–N(2)–O(2) 123.68(14), C(2)–N(2)–C(1) 114.74(15), O(2)–N(2)–C(1) 121.19(16), C(1)–N(1)–C(3) 113.50(16).

more favourable conjugation of the lone pair of the N(2) atom with the C(2)=O(3) carbonyl group.

In compound **4c**, the ordinary bonds O(3)–C(2) and O(4)–C(3) are somewhat different: the bond O(4)–C(3) [1.4203(14) Å] is longer than the bond O(3)–C(2) [1.3874(14) Å]. And *vice versa*, the bond O(3)–H(3) (0.873 Å) is longer than the bond O(4)–H(4) (0.823 Å). The length differences of these O–C and O–H bonds can be regarded as an argument toward the third stage of the mechanism of arylglyoxal condensation with *N*-hydroxyurea **2** (Scheme 1).

In a similar manner, the other hydantoins were obtained. *3-Hydroxy-5-(*p-*chlorophenyl)hydantoin* **5c**, monohydrate, yield 74%, colourless crystals, mp 132–134 °C (decomp.). ^{1}H NMR [$(CD_3)_2SO$] δ: 5.29 (s, 1H, CH), 7.38 [d, 2H, C(2)H, C(6)H, ^3J 8.4 Hz], 7.51 [d, 2H, C(3)H, C(5)H, ^3J 8.4 Hz], 8.77 (s, 1H, NH), 10.64 (br. s, 1H, OH). IR (ν/cm^{-1}): 3290 (NH), 1765 (C=O), 1720 (C=O). MS [FAB, H$^+$, *m/z*, I_{rel} (%)]: 229 [M + H]$^+$ (30.8), 227 [M + H]$^+$ (100). Found (%): C, 43.98; H, 3.85. Calc. for $C_9H_7N_2O_3Cl{\cdot}H_2O$ (%): C, 44.19; H, 3.71. *3-Hydroxy-5-(2′-thienyl)-hydantoin* **5d**, monohydrate, yield 62%, yellowish crystals, unstable, mp 107–108 °C (decomp.). ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ: 5.56 (s, 1H, CH), 7.07 [td, 1H, C(4)H, ^3J 5.1 Hz, ^4J 1.5 Hz], 7.17 [dd, 1H, C(3)H, ^3J 3.6 Hz, ^4J 1.5 Hz], 7.57 [dd, 1H, C(5)H, ^3J 5.1 Hz, ^4J 1.5 Hz], 8.91 (br. s, 1H, NH), 10.68 (br. s, 1H, OH). IR (ν/cm^{-1}): 3520 (OH), 3265 (NH), 1775 (C=O), 1723 (C=O). MS [EI, *m/z*, I_{rel} (%)]: 198 [M]$^+$ (37.3), 181 (51.0), 170 (19.1), 111 (100). Found (%): N, 12.73. Calc. for $C_7H_6N_2O_3S{\cdot}H_2O$ (%): N, 12.96.

‡ *Crystal data for* **4c**: crystals were grown from THF–C_6H_{14} at –20 °C, $C_9H_9ClN_2O_4{\cdot}2H_2O$, tetragonal, space group $P\bar{4}2_1c$, a = 17.1691(2), b = 17.1691(2) and c = 8.2700(1) Å, α = 90°, β = 90° and γ = 90°, V = 2437.81(5) Å^3, M_r = 280.66, Z = 8, d_{calc} = 1.529 g cm^{-3}, μ(MoKα) = = 0.336 mm^{-1}, F(000) = 1168.

Crystal data for **5a**: crystals were grown from THF–CH_2Cl_2 at –20 °C, $C_9H_8N_2O_3{\cdot}H_2O$, monoclinic, space group $P2_1/c$, a = 19.427(5), b = 6.1575(8) and c = 7.9395(11) Å, α = 90°, β = 96.132(15)°, γ = 90°, V = 944.3(3) Å^3, M_r = 210.19, Z = 4, d_{calc} = 1.479 g cm^{-3}, μ(MoKα) = 0.118 mm^{-1}, F(000) = = 440. X-ray diffraction study of compounds **4c** and **5a** was performed at 298 K on a Xcalibur 3 diffractometer (graphite monochtomated MoKα radiation, CCD detector, ω and φ-scans, 2θ = 64.94° for **4c** and 52.00° for **5a**). Structures were solved by direct methods and refined by a full-matrix least squares procedure in an anisotropic approximation for non-hydrogen atoms using the SHELX-97 program package.[7] Positions of non-hydrogen atoms were initially located from the difference electron density maps and further included into refinement in riding model approximation with U_{iso}(H) = nU_{eq}(carrier atom) with n = 1.5 for methyl, hydroxy groups and water molecules and n = 1.2 for the remaining H-atoms. In the structure of **4c** hydrogen atoms of O(4) hydroxy group and O(2W) water molecule were found to be disordered over two positions having equal occupancy. Refinement against F^2 in an anisotropic approximation (the hydrogen atoms isotropic in the riding model) by a full matrix least-squares method for 4299 reflections was carried out to wR_2 = 0.083 [R_1 = 0.031 for 3445 reflections with $F > 4\sigma(F)$, S = 1.06] for **4c** and for 1788 reflections was carried out to wR_2 = 0.064 [R_1 = 0.037 for 973 reflections with $F > 4\sigma(F)$, S = 1.00] for **5a**.

CCDC 659260 and 617196 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

Thus, this reaction of arylglyoxal with *N*-hydroxyurea is a new way to 3-hydroxy-5-arylimidazolidine-2,4-diones, but this kind of hydantoins cannot undergo spontaneous resolution by crystallization.

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