The first synthesis of assemblies of imidazolidine rings by α-ureidoalkylation of imidazolidin-2-one with 4,5-dihydroxyimidazolidin-2-ones

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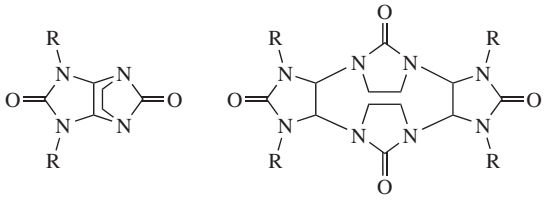
The synthesis of assemblies of imidazolidine rings has been developed based on the α-ureidoalkylation of imidazolidin-2-one with 4,5-dihydroxyimidazolidin-2-ones.

We have recently elaborated methods for the directed synthesis of alkyl-, hydroxyalkyl- and carboxyalkyl-substituted glycolurils, including enantiomerically pure compounds, by α-ureidoalkylation of alkylureas, ureidoalcohols, chiral and enantiomerically pure ureidoacids using 4,5-dihydroxyimidazolidin-2-ones as ureidoalkylating reagents.[1–6] Furthermore, similar reactions of sulfamides and thiosemicarbazide were studied and heteroanalogues of glycolurils, namely, 7-oxo-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octane 3,3-dioxides and 5,7-dialkyl-3-thioxooctahydroimidazo[4,5-*e*][1,2,4]triazin-6-ones were obtained.[7,8] Based on these results, it could be assumed that cyclic ureas, imidazolidin-2-one (ethyleneurea) in particular, can also undergo similar reactions with 4,5-dihydroxyimidazolidin-2-ones.

The purpose of this work was to study the α-ureidoalkylation of ethyleneurea with 4,5-dihydroxyimidazolidin-2-ones.

Previously, imidazolidin-2-one **1** has not been used in α-ureidoalkylation, though published data are available that it is a stronger nucleophile than urea.[9] It could be expected that the reaction of 4,5-dihydroxyimidazolidin-2-ones **2** with ethyleneurea **1** under the conditions of glycolurils synthesis would result in compounds **3** or **4**.

The α-ureidoalkylation of ethyleneurea **1** with 4,5-dihydroxyimidazolidin-2-ones **2a–c** aimed at possible synthesis of structures **3** or **4** was carried out under conditions of glycolurils synthesis, specifically, by refluxing equimolar amounts of the reagents in water at pH 1 for 1 h.[2] The reaction of compound **2a** with ethyleneurea **1** showed that a precipitate was formed after 15 min from the reaction mixture and the quantity of this precipitate increased with time. No precipitates were formed in reactions of compounds **2b**,**c** with ethyleneurea **1**. In the former case, the precipitate was filtered off after an hour and recrystallised from water. In the other two cases, the reaction mixtures were concentrated to oils, which were then solidified by treatment with a methanol–acetone mixture (2:1). The resulting precipitates were studied by ^{1}H NMR spectroscopy and mass spectrometry. The fragment ions with the highest molecular mass in the spectra of the precipitates corresponded to the molecular mass of compounds **3**, but the ^{1}H NMR spectra of these compounds contained proton signals the integral intensity of which contraindicated both of the proposed structures **3** or **4**. According to the ^{1}H NMR data, the integral intensity ratio of the main signal types (broadened singlets of CH_2–CH_2 groups at δ 3.35–3.50, singlets of CH–CH groups at δ 5.10–5.20 and singlets of NH groups at δ 6.70–6.75) was 4:1:1. Based on these data, we deduced that the compounds isolated were derivatives of 4,5-di-(2-oxoimidazolidin-1-yl)imidazolidin-2-one **5a–c**;† that is, the first



3 **4**

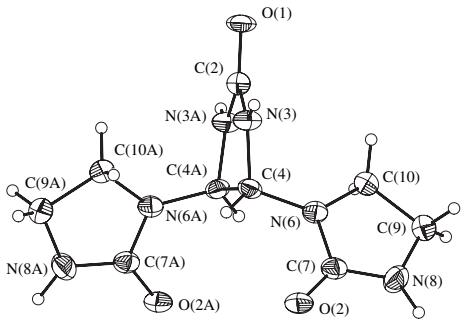
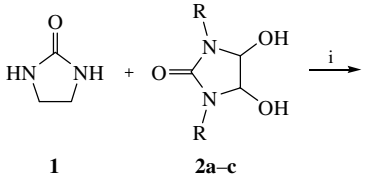


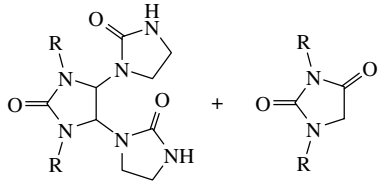
Figure 1 General view of the molecule of **5a**. Selected bond lengths (Å): O(1)–C(7) 1.230(3), O(2)–C(2) 1.248(4), C(2)–N(3) 1.349(3), C(4)–N(6) 1.435(3), C(4)–N(3) 1.454(3), N(8)–C(7) 1.340(3), N(8)–C(9) 1.439(4), N(6)–C(7) 1.365(3), N(6)–C(10) 1.459(3) and angles (º): C(7)–N(8)–C(9) 113.0(2), C(2)–N(3)–C(4) 111.6(2), C(7)–N(6)–C(4) 123.8(2), C(7)–N(6)–C(10) 111.9(2), C(4)–N(6)–C(10) 123.7(2).

representatives of assemblies of three imidazolidine rings. The yields of compounds **5a–c** were 21–26%. Furthermore, unreacted compounds **2a–c** and their rearrangement products, hydantoins[10] **6a–c** (Scheme 1), were isolated from the reaction mixtures.

The structure of compound **5a** was confirmed using X-ray analysis for a single crystal of **5a** as an example (Figure 1).† The X-ray analysis of **5a** undoubtedly revealed that the compound is an assembly of three imidazolidine rings (Figure 1). Compound **5a** crystallises as a racemate (space group *C*2/*c*) with two solvation water molecules and is characterised by C_2 symmetry with the *trans* arrangement of terminal imidazolidine rings with respect to the central ring [the torsion angle N(6)–C(4)–C(4A)–N(6A) is –142.5°]. The conformation of the central ring is a twist with the deviation of C(4) and C(4A) atoms by 0.19 Å, while the terminal ones are characterised by an envelope conformation with deviation of the C(9) atom by 0.11 Å.



1 **2a–c**



5a–c **6a–c**

a R = H
b R = Me
c R = Et

Scheme 1 *Reagents and conditions*: i, H_2O, pH 1–2, reflux, 1.5 h.

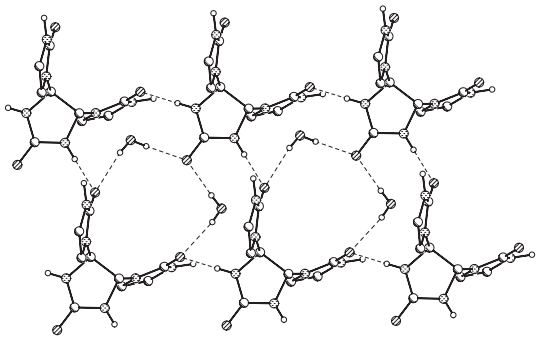
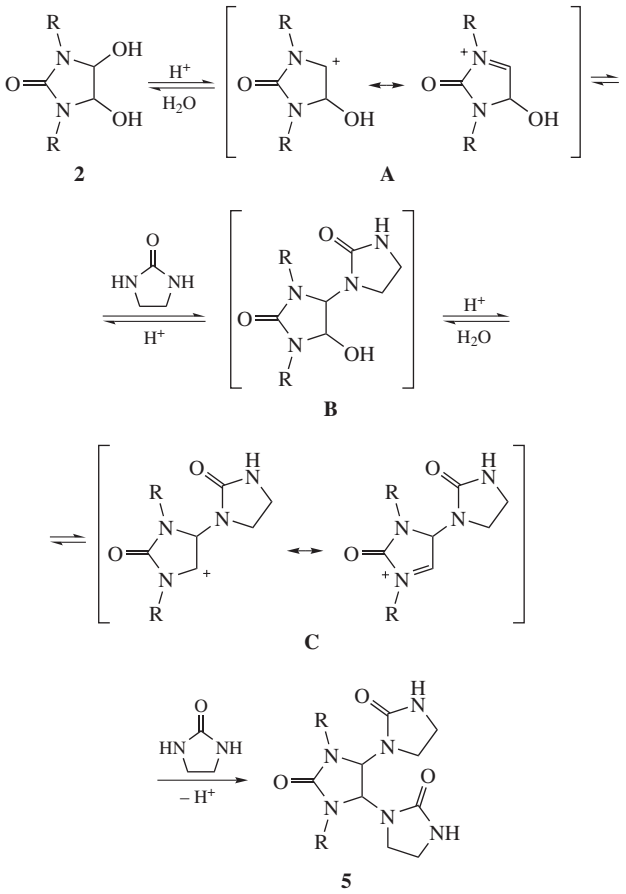


Figure 2 A fragment of H-bonded homochiral layer in the crystal structure of **5a**.

Analysis of crystal packing revealed that molecules of **5a** in the crystal are assembled by N–H···O bonds [N···O 2.897(2) Å] into H-bonded homochiral layers (Figure 2) parallel to the crystallographic *bc* plane and the H-bonded rings are centered by two water molecules O···O [2.796(2)–2.826(2) Å]. In addition, water molecules interlink the neighbouring layers by N–H···O bonds [N···O 2.861(2) Å].

The synthesis of these hitherto unknown structures was optimised for compound **5a** as an example. As expected, when the reaction was carried out with starting compounds **1** and **2a** under the same conditions but in a stoichiometric ratio, the yield of **5a** increased to 44%, while when the reaction time increased to 1.5 h, the yield of **5a** increased to 64%. After compound **5a** was separated, the ^{1}H NMR spectrum of the mother liquor evaporated to dryness did not contain proton signals from unreacted compounds **1** and **2a**, but only proton signals from hydantoin and unidentifiable oligomers were detected. The conditions found were used in reactions of ethyleneurea **1** with 1,3-dimethyl- and 1,3-diethyl-4,5-dihydroxyimidazolidin-2-ones **2b**,**c**. The yields of compounds **5b** and **5c** were 53 and 40%, respectively.



Scheme 2 Mechanism of formation of assemblies **5** of three imidazolidine rings.

The formation of assemblies of imidazolidine rings **5** instead of expected tricyclic structures **3** is probably due to the rigidity of the molecular frame of original ethyleneurea **1**, which prevents the second NH group from entering into cyclocondensation. An attempt to obtain tetracyclic system **4** by the condensation of resulting **5b** with **2a** yielded polymers, apparently due to the *trans* orientation of the imidazolidine rings at the 4- and 5-positions of compound **5b**.

Based on the mechanism[3] of formation of glycolurils *via* the α-ureidoalkylation of ureas with 4,5-dihydroxyimidazolidin-2-ones, the formation of compounds **5** can be assumed to occur as two-step α-ureidoalkylation of imidazolidin-2-one **1** with 4,5-dihydroxyimidazolidin-2-ones **2** (Scheme 2).

At the first reaction stage, the protonation of compound **2** and the elimination of one water molecule gives carbonium-immonium ion **A** (shown as two resonance structures) that condenses with the first molecule of ethyleneurea **1**. At the second reaction stage, resulting intermediate **B**, that is, an α-ureidoalkylating reagent, undergoes protonation and dehydration to carbonium-immonium ion **C**, which reacts with another molecule of ethyleneurea **1** to give compound **5**.

Thus, a study of the α-ureidoalkylation of imidazolidin-2-one **1** using 4,5-dihydroxyimidazolidin-2-ones **2** as ureidoalkylating reagents resulted in hitherto unknown assemblies of three imidazolidine rings, the structures of which were confirmed by a combination of spectroscopic characteristics and X-ray data.†

† All new compounds gave satisfactory elemental analyses. Their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz). Chemical shifts were measured with reference to the residual protons of a [$^2H_6$]DMSO solvent (δ 2.50 ppm). Mass spectra were measured on an MS 30 spectrometer.

General procedure for the synthesis of 1,3-dihydro- and 1,3-dialkyl-4,5-di(2-oxoimidazolidin-1-yl)imidazolidin-2-ones **5a–c**. A catalytic amount of hydrochloric acid (pH 1) was added to a solution of ethyleneurea **1** (imidazolidin-2-one) (0.02 mol) and corresponding 4,5-dihydroxyimidazolidin-2-one **2a–c** (0.01 mol). The reaction mixture was refluxed for 1.5 h. In the case of compound **5a**, the precipitate formed was filtered off and recrystallised from water. The yield of **5a** was 64%. In the case of compounds **5b**,**c**, the reaction mixtures were concentrated into oils and solidified with a methanol–acetone mixture. The resulting precipitates were recrystallised from MeOH. The yields were 53 and 40%, respectively.

5a: yield 61–64%, mp 250–252 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.35 (m, 8H, CH_2CH_2), 5.17 (s, 2H, CHCH), 6.50 (br. s, 2H, 2NH), 6.90 (s, 2H, 2NH). MS, *m*/*z* (%): 168 (5, M^+ – 86), 86 (100), 69 (8), 56 (11).

5b: yield 50–53%, mp 263–264 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.61 (s, 6H, NMe), 3.40 (m, 8H, CH_2CH_2), 5.10 (s, 2H, CHCH), 6.75 (br. s, 2H, 2NH). MS, *m*/*z* (%): 196 (100, M^+ – 86), 141 (10), 128 (11), 112 (12), 97 (9), 86 (8), 70 (10).

5c: yield 37–40%, mp 270–273 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.10 (m, 6H, 2Me), 2.75 (m, 2H, $2CH_2$), 3.11 (m, 2H, $2CH_2$), 3.37 (m, 8H, CH_2CH_2), 5.20 (s, 2H, CHCH), 6.70 (s, 2H, 2NH). MS, *m*/*z* (%): 224 (63, M^+ – 86), 196 (15), 168 (14), 140 (33), 127 (25), 113 (27), 97 (31), 86 (100), 83 (32), 70 (62), 69 (37), 60 (18).

X-ray diffraction analysis: at 120 K crystals of **5a** ($C_9H_{18}N_6O_5$) are monoclinic, space group *C*2/*c*, a = 11.759(2), b = 9.335(2), c = 11.386(3) Å, β = 92.977(6)°, V = 1248.2(5) Å^3, Z = 4 (Z' = 0.5), M = 290.29, d_{calc} = 1.545 g cm^{-3}, μ(MoKα) = 1.27 cm^{-1}, F(000) = 616. Intensities of 2478 reflections were measured with a Smart 1000 CCD diffractometer at 120 K ($2\theta < 54°$), and 1285 independent reflections (R_{int} = 0.04711) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atoms were located from the Fourier density synthesis. The refinement converged to wR_2 = 0.1020 and GOF = 0.917 for all independent reflections [R_1 = 0.0504 was calculated against F for 684 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 603575. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2006.

These studies can be of not only theoretical but also practical value since it is known that imidazolidin-2-one derivatives exhibit a directed effect on the central nervous system, as well as herbicidal and insecticidal activities.[11–13]

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