

## New conglomerate in the series of glycoluriles

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Three new chiral glycoluriles with a 2-(3-carboxypropyl) substituent were synthesised and characterised by X-ray diffraction analysis; one of them, 4-{3,7-dioxo-2-(3-carboxypropyl)-6,8-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl}butanoic acid, was found to crystallise as a conglomerate.

Chiral glycoluriles (2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-diones) can crystallise as conglomerates (*i.e.*, as the mixture of homochiral crystals of enantiomers). In particular, 2,6-dimethyl- and 2,6-diethylglycoluriles belong to such compounds.<sup>1–3</sup> Since glycoluriles are psychotropically active compounds,<sup>4–6</sup> a search of the pathways for their resolution into enantiomers is necessary for the development of chiral drugs. The formation of conglomerates is the simplest way for obtaining enantiomerically pure compounds, and we carry out a search of new conglomerates in the series of chiral glycoluriles. An approach to such a kind of glycoluriles could be the introduction of substituents at nitrogen atoms of functional groups capable to form hydrogen bonds, *e.g.*, carboxylic groups, which will lead to the desired homochiral supramolecular assembling of molecules.

Recently,<sup>7</sup> we synthesised such a kind of structures by cyclocondensation of 4,5-dihydroxyimidazolidin-2-one **1a** with monosubstituted ureas containing different functional groups in the composition, including the carboxyl group. On the basis of that approach, we synthesised racemic glycoluriles **3b** and **3c** by cyclocondensation of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones **1b,c** with 1-(carboxypropyl)urea **2** (Scheme 1).<sup>†</sup> However, compounds **1b** and **1c** more difficultly react with **2** than compound **1a** and only heating for 2 h yielded desired glycoluriles **3b,c**.

To elucidate the capability of synthesised racemic glycoluriles **3b,c**, as well as of **3a**, obtained according to the method,<sup>7</sup> to crystallise as conglomerates, their crystals were grown by crystallization from water. The crystals of compounds **3a** and **3c** are thin needles, and the crystals of compound **3b** of different shapes were obtained. The crystals of a wedge form (**3b'**) have  $[\alpha]_D = +21.92^\circ$ , and the crystals of a square plate form (**3b''**) have  $[\alpha]_D = -18.68^\circ$ . The other physico-chemical characteristics of **3b'** and **3b''** are identical; thus, racemate ( $\pm$ )-**3b** crystallises from water as a conglomerate.

The X-ray diffraction study<sup>‡</sup> of compounds **3a**, **3c** and **3b''** supported this probability: only **3b''** crystallises in chiral space group  $P2_1$ , while **3a** and **3c** crystallise as racemates (space groups  $P2_1/c$  and  $Pbca$ ). It should be noted that **3a** crystallises as a monohydrate with two independent molecules and two independent water molecules.

Despite of the above difference, an analysis of the crystal packing surprisingly revealed that, although space groups of

**3b''** and **3c** are different, the general features of their supramolecular organization are practically the same. In contrast, the presence of a great number of active centres, which are capable for H-bond formation, as well as the presence of water molecules in **3a**, leads to different crystal packing patterns.

In the crystal of **3a**, molecules are assembled into heterochiral chains by means of N–H...O bonds [N...O 2.817(3)–2.942(3) Å], which are cross-linked by N–H...O=C–OH bonds [N...O 2.823(3)–2.881(3) Å] into the layers (Figure 1). Note that such heterochiral chains are close to the tetramers, which were observed earlier in the co-crystal of 2,6-dimethylglycolurile and 2,8-dimethylglycolurile.<sup>2</sup> Water molecules assemble the above layers into a three-dimensional H-bonded framework, forming O–H...O=C bonds [O...O 2.737(2)–2.767(3) Å] with carboxamide groups and serving as proton donors in H-bonds with the carboxy group [O...O 2.568(3)–2.614(3) Å].

In the crystals of **3b''** and **3c** H-bonds assemble molecules into practically identical homochiral corrugated layers (Figure 2). In the layer, each molecule is surrounded by four neighbours

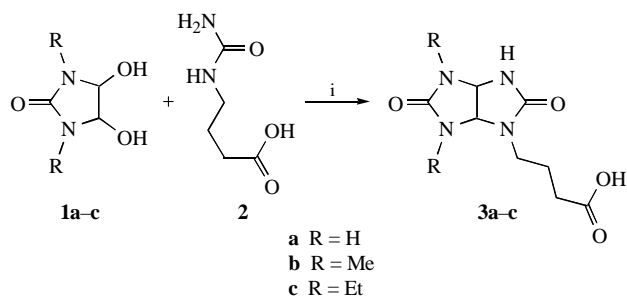
<sup>†</sup> All new compounds exhibited satisfactory elemental analyses, and their structures were confirmed by IR, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker WM-250 (250 MHz) and Bruker AM-300 (75.5 MHz) spectrometers, respectively. Chemical shifts were measured with reference to the residual protons of a [<sup>2</sup>H<sub>6</sub>]DMSO solvent ( $\delta$  2.50 ppm). Mass spectra were measured on an MS 30 spectrometer. Optical rotation was measured on a Polamat-A polarimeter.

Initial 4,5-dihydroxyimidazolidin-2-one **1a**, 1,3-dimethyl-4,5-dihydroxyimidazolidin-2-one **1b** and 1,3-diethyl-4,5-dihydroxyimidazolidin-2-one **1c** were synthesised according to a known method from glyoxal and urea,<sup>8</sup> 1,3-dimethyl-<sup>9</sup> and 1,3-diethylurea,<sup>10</sup> respectively. *N*-Carbamoyl- $\gamma$ -aminobutanoic acid **2** was synthesised analogously from  $\gamma$ -aminobutanoic acid and KOCN.<sup>7</sup>

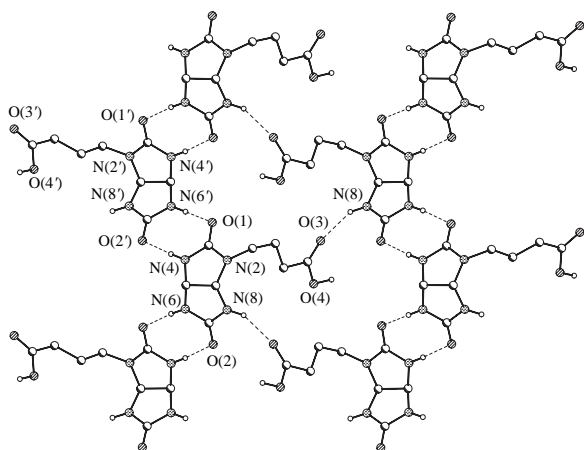
Two kinds of crystals [wedge plates (17.2 mg) and square plates (5.1 mg)] possessing optical activity were prepared by crystallization of ( $\pm$ )-**3b** from water. For wedge plate crystals of **3b'**,  $[\alpha]_D = +21.92^\circ$  (*c* 1.31, H<sub>2</sub>O). The second kind of square plate crystals of **3b''** was divided into two parts. For a greater part,  $[\alpha]_D = -18.68^\circ$  (*c* 0.38, H<sub>2</sub>O). A smaller part was used for X-ray diffraction analysis.<sup>‡</sup>

4-{3,7-Dioxo-2-(3-carboxypropyl)-6,8-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl}butanoic acid **3b'** and **3b''**: yield 45%, mp 232–233 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO)  $\delta$ : 1.57–1.90 (m, 2H, CCH<sub>2</sub>C), 2.21 (t, CH<sub>2</sub>CO, <sup>3</sup>J 7.3 Hz), 2.64 (s, 3H, Me), 2.81 (s, 3H, Me), 2.97–3.35 (m, 2H, CH<sub>2</sub>), 5.07, 5.19 (dd, 2H, CH–CH, <sup>3</sup>J 7.9 Hz), 7.63 (s, 1H, NH), 12.08 (br. s, 1H, COOH). <sup>13</sup>C NMR ([<sup>2</sup>H<sub>6</sub>]DMSO)  $\delta$ : 22.9 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 30.8 (Me), 41.0 (Me), 66.7 (CH), 71.3 (CH), 158.5 (CO), 159.5 (CO), 174.2 (CO). MS, *m/z* (I, %): 256 (M<sup>+</sup>, 3), 183 (10), 153 (48), 140 (36), 127 (18), 113 (26), 112 (100), 97 (14), 85 (15), 69 (19), 56 (36).

4-{3,7-Dioxo-2-(3-carboxypropyl)-6,8-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl}butanoic acid **3c**: yield 40%, mp 187–189 °C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO)  $\delta$ : 0.98–1.06 (m, 6H, 2Me), 1.58–1.83 (m, 2H, CCH<sub>2</sub>C), 2.21 (t, CH<sub>2</sub>CO, <sup>3</sup>J 7.3 Hz), 2.98–3.46 (m, 6H, 3CH<sub>2</sub>), 5.21, 5.32 (dd, 2H, CH–CH, <sup>3</sup>J 8.5 Hz), 7.62 (s, 1H, NH), 12.11 (br. s, 1H, COOH). <sup>13</sup>C NMR ([<sup>2</sup>H<sub>6</sub>]DMSO)  $\delta$ : 13.0 (Me), 13.1 (Me), 22.8 (CH<sub>2</sub>), 30.8 (CH<sub>2</sub>), 35.6 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub>), 40.9 (CH), 63.8 (CH), 68.6 (CH), 157.7 (CO), 159.5 (CO), 174.2 (CO). MS, *m/z* (I, %): 284 (M<sup>+</sup>, 5), 211 (6), 182 (23), 170 (19), 145 (100), 127 (17), 111 (17), 97 (19), 85 (17), 84 (28), 69 (35), 57 (32), 56 (70).



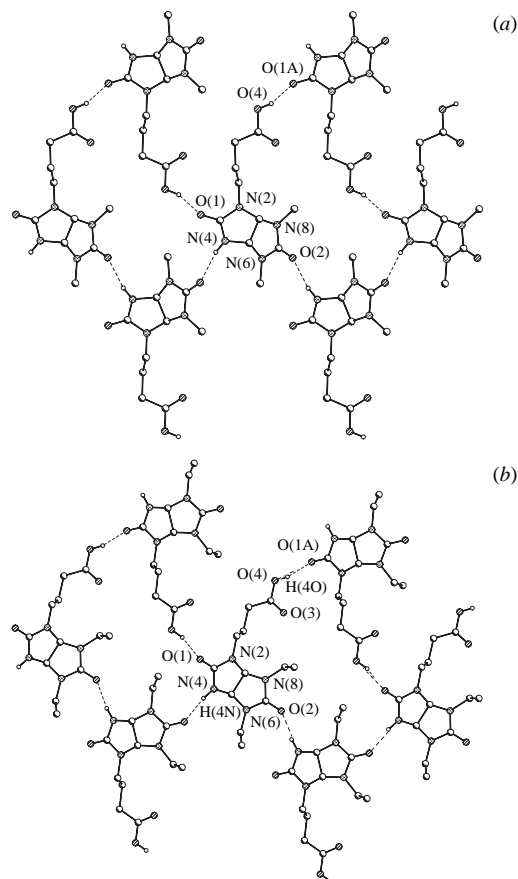
Scheme 1 Reagents and conditions: i, H<sub>2</sub>O, pH 1–2, 80 °C, 2 h.



**Figure 1** Heterochiral layers in the crystal structure of **3a**. The water molecules are omitted for clarity.

and forms two N–H...O=CN<sub>2</sub> [N...O 2.780(3)–2.865(3) Å] and two O=C–O–H...O=CN<sub>2</sub> [O...O 2.630(3)–2.639(3) Å] H-bonds. Thus, the carboxy group serves as the donor of protons, and the O(3) atom does not participate in specific intermolecular interactions. The only difference in the crystal packings of **3b''** and **3c** is that in **3b''** layers have the same chirality, while in **3c** their alternate leading to a racemate crystal. Note that the analysis of intermolecular contacts did not reveal specific interactions, which can stabilise the homochiral packing in the case of **3b''**.

The comparison of molecular geometries revealed that bond lengths and angles in **3a–c** are similar (Figure 3). The five-membered rings are characterised by a flattened envelope conformation with the deviation of nitrogen or C(1)/C(5) atoms by



**Figure 2** Homochiral corrugated layer in the crystals of (a) **3b''** and (b) **3c**.

‡ *Crystallographic data for compounds 3a, 3b'' and 3c.*

The crystal of **3a** (C<sub>8</sub>H<sub>14</sub>N<sub>4</sub>O<sub>5</sub>) is monoclinic at 110 K, space group *P2<sub>1</sub>*, *a* = 9.033(2), *b* = 10.090(2), *c* = 24.733(4) Å, β = 98.922(4)°, *V* = 2226.9(7) Å<sup>3</sup>, *Z* = 8 (*Z'* = 2), *M* = 246.23, *d*<sub>calc</sub> = 1.469 g cm<sup>-3</sup>, μ(MoKα) = 1.23 cm<sup>-1</sup>, *F*(000) = 1040.

The crystal of **3b''** (C<sub>10</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>) is monoclinic at 298 K, space group *P2<sub>1</sub>*, *a* = 6.013(1), *b* = 10.704(2), *c* = 9.658(2) Å, β = 100.24(3)°, *V* = 611.7(2) Å<sup>3</sup>, *Z* = 2 (*Z'* = 1), *M* = 256.27, *d*<sub>calc</sub> = 1.391 g cm<sup>-3</sup>, μ(MoKα) = 1.09 cm<sup>-1</sup>, *F*(000) = 272.

The crystal of **3c** (C<sub>12</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>) is orthorhombic at 298 K, space group *Pbca*, *a* = 11.651(2), *b* = 9.324(2), *c* = 26.859(5) Å, *V* = 2918(1) Å<sup>3</sup>, *Z* = 8 (*Z'* = 1), *M* = 284.32, *d*<sub>calc</sub> = 1.294 g cm<sup>-3</sup>, μ(MoKα) = 0.98 cm<sup>-1</sup>, *F*(000) = 1216.

Intensities of 22610 (**3a**) were measured with a Smart 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scan with a 10 s exposure, 2θ < 56°] at 120 K and 1994 (**3b''**), 2564 (**3c**) reflections were measured with Siemens P3/PC [λ(MoKα) = 0.71072 Å, θ/2θ scan, 2θ < 60° (**3b''**) and 52° (**3c**)] at 298 K. 5350 (**3a**), 1994 (**3b''**) and 2564 (**3c**) independent reflections were used in the further refinement. The structures were solved by a direct method and refined by the full-matrix least-squares technique against *F*<sup>2</sup> in the anisotropic-isotropic approximation. The analysis of the Fourier synthesis has revealed that in the one of the independent molecules in **3a** the butyl group is disordered with occupancies 0.8 and 0.2.

The refinement converged to *wR*<sub>2</sub> = 0.1507 and GOF = 1.043 for all independent reflections [*R*<sub>1</sub> = 0.0596 was calculated against *F* for 2374 observed reflections with *I* > 2σ(*I*)] for **3a**; to *wR*<sub>2</sub> = 0.0958 and GOF = 0.951 for all independent reflections [*R*<sub>1</sub> = 0.0364 was calculated against *F* for 1496 observed reflections with *I* > 2σ(*I*)] for **3b''** and to *wR*<sub>2</sub> = 0.0745 and GOF = 0.913 for all independent reflections [*R*<sub>1</sub> = 0.0426 was calculated against *F* for 998 observed reflections with *I* > 2σ(*I*)] for **3c**. 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.ac.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 numbers 238617–238619. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

at least 0.07 Å. The dihedral angle between the planes of five-membered rings varied in the range 119.7–122°.

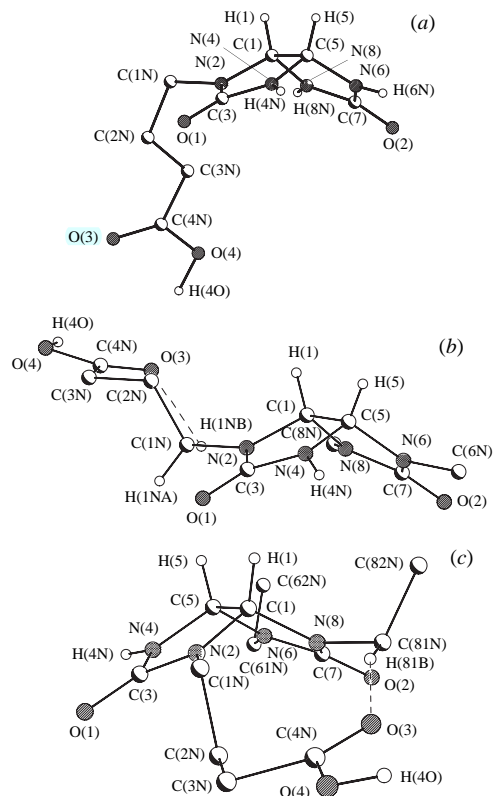
The main difference in the above series of compounds is observed for the conformation of a γ-carboxypropyl substituent. In **3a**, the conformation of the caboxypropyl fragment is antiperiplanar [the torsion angles C(1N)C(2N)C(3N)C(4N) are 176–179°], and the C=O groups in two independent molecules are in *syn*-periplanar and *anti*-periplanar conformations in respect to the C(3N)–C(2N) bond [the torsion angle O(3)C(4N)C(3N)–C(2N) is equal to 4.9 and 153.5°].

In contrast, in **3b''** and **3c**, the γ-carboxypropyl fragment is characterised by a synclinal conformation [the torsion angle C(1N)C(2N)C(3N)C(4N) is 76.1–78.7°] and the C=O group is in the *syn*-periplanar conformation in respect to the C(3N)–C(2N) bond [the torsion angle O(3)C(4N)C(3N)C(2N) is 2.3–14.2°]. Such a conformation of the γ-carboxypropyl substituent in **3b''** and **3c**, probably, is the result of the formation of intramolecular C–H...O contacts, namely, C(1N)–H(1N)...O(3) and C(81N)–H(81NB)...O(3) (H...O 2.49–2.51 Å). Although the conformations of γ-carboxypropyl in **3b''** and **3c** are similar, its orientation in respect to bridgehead hydrogens is different. In **3c**, as well as in **3a**, this fragment is oriented inside the bicycle, while in **3b''** it is characterised by the *trans*-configuration in respect to H(1) and H(5) atoms (Figure 3).

Probably, this difference in the orientation of the γ-carboxypropyl substituent leads to the formation of a racemic crystal in the case of **3c**. Namely, the homochiral packing in this crystal inevitably leads to the repulsion of ethyl and γ-carboxypropyl groups.

Thus, the formation of homochiral supramolecular layers can be considered as a necessary but insufficient condition for crystallization as a conglomerate.

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**Figure 3** The general view of (a) **3a** (one of independent molecules), (b) **3b''** and (c) **3c**.

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