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Synthesis of (*S*)-*N*-hydantoinoalkylglycoluriles by one-pot double cyclisation of chiral α,ω-diureido acids under the action of 4,5-dihydroxyimidazolidin-2-ones

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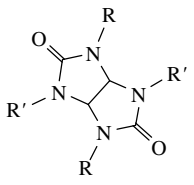
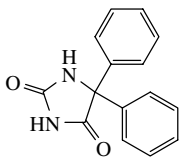
The reaction of 4,5-dihydroxyimidazolidin-2-ones with chiral (*S*)-*N*,*N*′-dicarbamoyl-α,ω-amino acids occurs as one-pot double cyclisation under acid catalysis to give the corresponding glycoluriles with (*S*)-*N*-hydantoinoalkyl substituents.

The search for new medicines affecting the central nervous system is of current interest. N-Substituted glycoluriles (or bicyclic bisureas), which possess a broad spectrum of pharmacological effects, are promising psychotropic substances.[1,2] Mebicar, an efficient day-time tranquilizer, was the first representative of this class introduced into practice in 1979.[1] Albicar is at an earlier stage of implementation.[2] Of monocyclic urea derivatives, which possess different kinds of pharmacological activity, the derivatives of imidazolidine-2,4-dione (hydantoin), in particular, diphenin (5,5-diphenylhydantoin), which has an anticonvulsant effect, should be distinguished.[1,3] New medicines can be obtained either by preparing different combinations of known drugs[4] or by synthesising new compounds that contain several pharmacophoric fragments within a molecule.[1] In this work, we studied the preparation of structures that simultaneously contain glycolurile and hydantoin fragments.



Mebicar: R = R′ = Me
Albicar: R = Me, R′ = Et

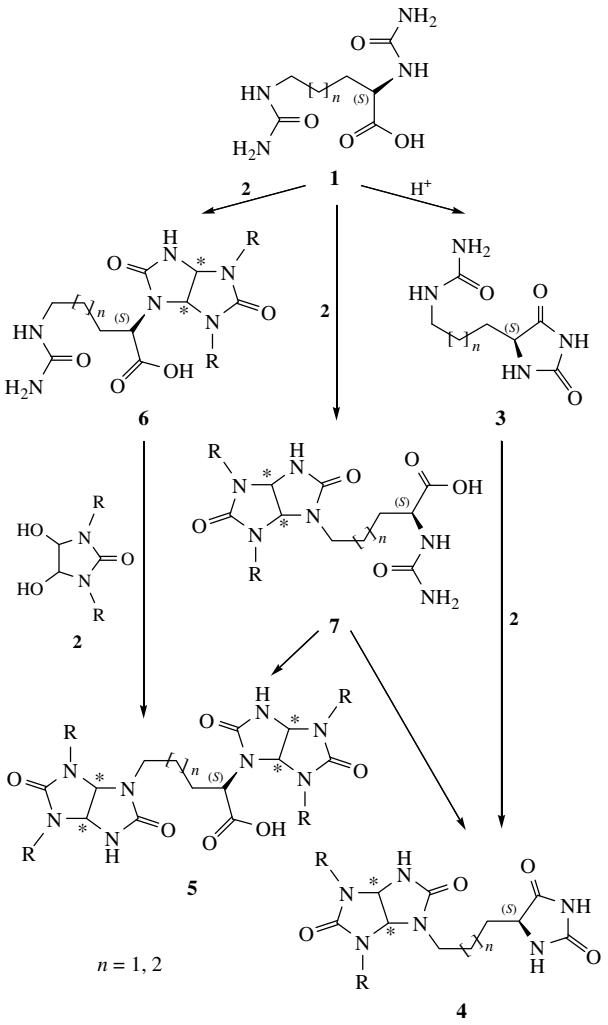


Diphenin

The α-ureidoalkylation of mono- and disubstituted ureas by treatment with 4,5-dihydroxyimidazolidin-2-ones[5,6] is regarded as a general method for the synthesis of glycoluriles. Using this approach, we have recently performed diastereoselective[6] and diastereospecific[7] syntheses of chiral glycoluriles by the cyclocondensation of 4,5-dihydroxyimidazolidin-2-ones with chiral α-ureidoacids. The diastereospecific synthesis was carried out under homogenous acid catalysis at pH 1 and 80 °C. On the other hand, α-ureidoacids and their derivatives can be converted to 5-substituted hydantoins by cyclisation under either acid or alkaline catalysis.[8–10] In particular, 5-[3-carbamoylaminopropyl-(butyl)]imidazolidine-2,4-diones **3** were obtained by cyclisation of α-*N*-carbamoyl-(*S*)-citrulline(lysine) **1a**(**b**) at pH 1.[10]

Taking into account these data, one might expected the formation of target *N*-hydantoinoalkylglycoluriles **4** in a one-pot reaction of compound **1** with 4,5-dihydroxyimidazolidin-2-ones **2** at pH 1. This assumption follows from the following facts. Cyclisation of the α-ureidoacid fragment in α,ω-diureidoacids **1** can result in formation of the hydantoin part of compounds **4**, while the reaction of the ω-ureide fragment with 4,5-dihydroxyimidazolidin-2-ones **2** can result in the glycolurile part of compounds **4**. It is reasonable to perform this process in two stages; that is, first to obtain hydantoins **3** and then, to perform their cyclocondensation with 4,5-dihydroxyimidazolidin-2-ones **2** without isolation. However, we could not rule out competitive reactions, in which the ureide fragments of α,ω-diureidoacids **1** react with 4,5-dihydroxyimidazolidin-2-ones **2** to give ureidoalkylglycoluriles **6** or **7**, which, in turn, can undergo cyclocondensation with the second molecule of compound **2** to give alkylenebis(glycolurile)carboxylic acids **5** (Scheme 1).

In order to assess the reactivity of α,ω-ureide fragments in α,ω-diureidoacids **1** and assuming the possible competitive formation of compounds **6** or **7**, we calculated the charges on



Scheme 1 Possible transformations of α,ω-diureidoacids **1**.

the nitrogen atoms in the α- and ω-ureide fragments of these compounds by the MNDO method using the MOPAC software complex.[11] The data (Figure 1) suggest that the charge distribution and magnitudes at the nitrogen atoms of the α- and ω-ureide fragments of **1a** are virtually the same and thus none of the reaction centres is preferable. The same conclusion can be made from a comparison of calculated data for compounds **6a** (R = H) and **7a** (R = H).

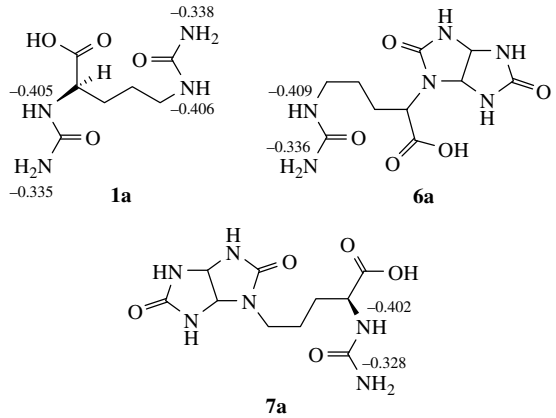


Figure 1 Calculated charges on the atoms of compounds **1a**, **6a** and **7a** (MNDO).

α,ω-Diureidoacids **1a**,**b** were synthesised by the reaction of commercially available (*S*)-citrulline and (*S*)-lysine with KCNO by analogy with reported procedures.[10] The molecule of (*S*)-citrulline already contains an ω-ureide fragment; therefore, 1 mol of KCNO was taken to introduce the α-ureide fragment. α,ω-Diureidoacid **1b** was obtained by the reaction of (*S*)-lysine with 2 mol of KCNO.

Resulting compounds **1a**,**b** were brought into reaction with equimolar amounts of 4,5-dihydroxyimidazolidin-2-ones **2a**,**b** under conditions similar to those of diastereospecific reactions[7] to give compounds **4a**,**b** (Scheme 2). The structures of the compounds obtained were determined from ^{1}H and ^{13}C NMR data.† The signals in the spectra were assigned using highly sensitive HMQC[12] and HMBC[13] inversion techniques.

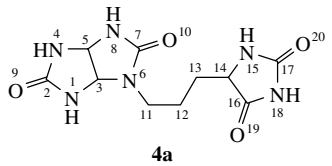
The ^{1}H NMR spectra of the compounds obtained in the diastereoselective synthesis of glycoluriles by the reaction of 4,5-dihydroxyimidazolidin-2-ones with enantiomers of α-ureidoacids[6] showed doubling of proton signals. Such a doubling is not observed in the ^{1}H NMR spectra of compounds **4**. Since the asymmetric centre in the starting diureidoacids is rather distant from the ureide fragments involved in the reaction, we can

† All new compounds exhibited satisfactory elemental analyses, and their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H and ^{13}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 [$^2H_6$]DMSO solvent (δ 2.50 ppm).

The initial 4,5-dihydroxyimidazolidin-2-ones **2** have been synthesised according to a known method from urea and glyoxal.[16]

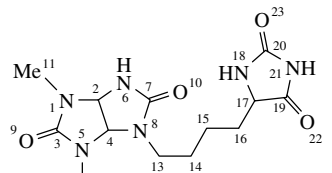
N$^\alpha$-*Carbamoyl-(*S*)-citrulline* **1a**: yield 54%, mp 165–168 °C (decomp.), ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.32–1.60 (m, 4H, 2CH$_2$), 2.91–2.97 (m, 2H, CH$_2$), 3.98–4.07 (m, 1H, CH), 5.41 (br. s, 2H, NH$_2$), 5.61 (br. s, 2H, NH$_2$), 6.07 (t, 1H, NH, ^3J 5.5 Hz), 6.29 (d, 1H, NH, ^3J 7.9 Hz), 13.56 (br. s, 1H, COOH).

N,N′-*Dicarbamoyl-(*S*)-lysine* **1b**: yield 54%, mp 174–176 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.26–1.36 (m, 4H, 2CH$_2$), 1.57 (m, 2H, CH$_2$), 2.97 (m, 2H, CH$_2$), 3.98 (m, 1H, CH), 5.27 (br. s, 4H, 2NH$_2$), 6.53 (br. s, 2H, 2NH), 12.41 (br. s, 1H, COOH).



4a

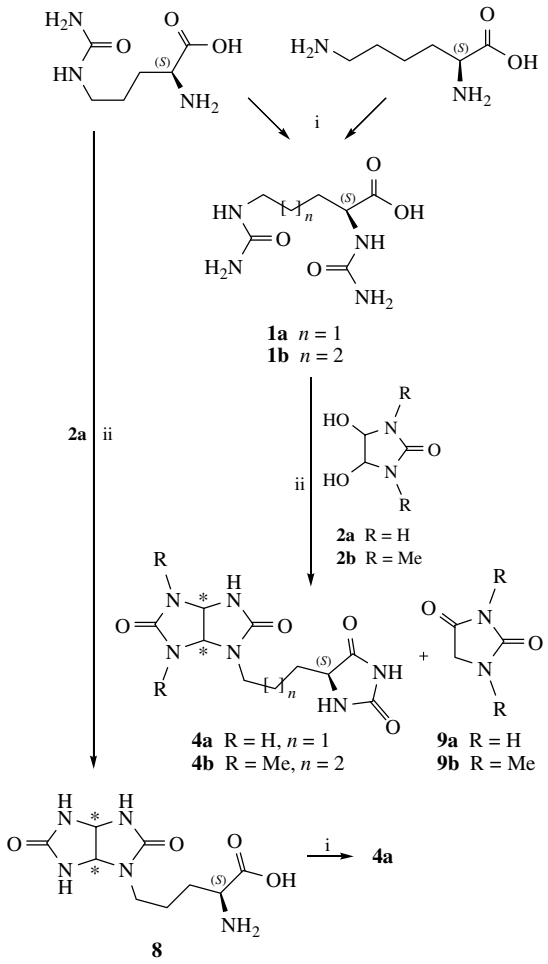
*2-{3-[2,5-Dioxoimidazolidin-4(*S*)-yl]propyl}{(1*R*,5*S*+1*S*,5*R*)-(2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione)}* **4a**: yield 54%, mp 223 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.38–1.61 (m, 4H, C^{12}H$_2$, C^{13}H$_2$), 2.92–3.18 (m, 2H, C^{11}H$_2$), 3.98 (br. s, 1H, C^{14}H), 5.16–5.24 (br. m, 2H, C^{3}H, C^{5}H), 7.26 (br. s, 2H, N^{4}H, N^{8}H), 7.39 (s, 1H, N^{1}H), 7.93 (s, 1H, CON^{15}H), 10.60 [s, 1H, (CO)$_2$N^{18}H]. ^{13}C {^{1}H} NMR ([$^2H_6$]DMSO) δ: 22.8 (C^{12}H$_2$), 28.8 (C^{13}H$_2$), 39.6 (C^{11}H$_2$), 57.3 (C^{14}H), 62.4 (C^{5}H), 67.7 (C^{3}H), 157.6 (C^{17}O), 159.4 (C^{7}O), 161.3 (C^{2}O), 176.2 (C^{16}O).



4b

*6,8-Dimethyl-2-{4-[2,5-dioxoimidazolidin-4(*S*)-yl]butyl}{(1*R*,5*S*+1*S*,5*R*)-(2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione)]* **4b**: yield 47%, mp 236 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.31–1.68 (m, 6H, C^{14}H$_2$, C^{15}H$_2$, C^{16}H$_2$), 2.65 (s, 3H, C^{12}H$_3$), 2.82 (s, 3H, C^{11}H$_3$), 3.02–3.37 (m, 2H, C^{13}H$_2$), 4.00 (br. s, 1H, C^{17}H), 5.10 (d, 1H, C^{4}H, ^3J 8.5 Hz), 5.19 (d, 1H, C^{2}H, ^3J 8.5 Hz), 7.60 (s, 1H, N^{6}H), 7.93 (s, 1H, CON^{18}H), 10.57 [s, 1H, (CO)$_2$N^{21}H]. ^{13}C {^{1}H} NMR ([$^2H_6$]DMSO) δ: 21.7 (C^{15}H$_2$), 27.1 (C^{14}H$_2$), 27.9 (C^{12}H$_3$), 29.7 (C^{11}H$_3$), 31.0 (C^{16}H$_2$), 41.4 (C^{13}H$_2$), 57.5 (C^{17}H), 65.6 (C^{4}H), 71.1 (C^{2}H), 157.5 (C^{20}O), 158.3 (C^{3}O), 159.4 (C^{7}O), 176.1 (C^{19}O).

*2-Amino-5-[(1*R*,5*S*+1*S*,5*R*)-(3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]-oct-2-yl)]-2(*S*)-pentanoic acid* **8**: yield 57%, mp 290–293 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.31–1.80 (m, 3CH$_2$), 2.81–3.06 (m, CH), 5.17–5.27 (m, 2H, 2CH), 7.29 (s, 1H, NH), 7.32 (s, 1H, NH), 7.54 (s, 1H, NH). ^{13}C {^{1}H} NMR (CD$_3$OD) δ: 22.5 (CH$_2$), 27.3 (CH$_2$), 40.2 (CH$_2$), 54.0 (CHNH$_2$), 63.2 (CH), 69.1 (CH), 161.2 (CO), 163.2 (CO), 174.00 (COOH).



Scheme 2 *Reagents and conditions*: i, H_2O, KCNO, pH 1, 100 °C, 1 h; ii, H_2O, pH 1, ~80 °C, 1 h.

assume that the reaction products **4** consist of diastereomeric mixtures with (1*R*,5*S*) and (1*S*,5*R*) configurations of the C(1) and C(5) bridging asymmetric atoms in the glycolurile fragment. The asymmetric atom of the hydantoin fragment retains the (*S*)-configuration of the original α-amino acid since the asymmetric centre is not affected under the reaction conditions.

In order to make sure that the revealed reaction direction is the only possible direction, we carried out the reaction of compound **1a** with two equivalents of **2a**, which could yield compound **5a**. Various reaction conditions were used: water, methanol or water + methanol as the solvent; the temperature was varied from 40 to 90 °C; the duration ranged from 0.5 to 12 h; different quantities of hydrochloric acid were added (pH 1–5). The progress of the reaction was monitored by taking samples of the reaction mixture at regular time intervals. The samples were evaporated to dryness and studied by ^{1}H NMR spectroscopy. It was found that glycolurile **4a** with a hydantoin substituent was the main product under the test conditions. At pH > 3 and temperatures below 40 °C, the reaction between the starting compounds was not observed even after 12 h. As regards by-products, the ^{1}H NMR spectra contained signals of hydantoin **9a**, which resulted from a rearrangement of 4,5-dihydroxyimidazolidin-2-one **2a**.

The data suggest that the direct α-ureidoalkylation of starting compound **1a** does not occur under the test conditions. Therefore, we tried yet another variant of the possible formation of compound **5a** in the case of (*S*)-citrulline. At first, it was treated with 4,5-dihydroxyimidazolidin-2-one **2a** under conditions reported previously[7] to give glycolurile **8**, which was not described before. The latter compound was treated with KCNO in order to create the ω-ureide fragment. However, product **4a** was obtained instead of expected compound **6a** (Scheme 2). Apparently, cyclisation into hydantoin occurs immediately after the N-carbamoylation upon acidification of the reaction mixture to pH ~1, which is required at the last stage of isolation of ureidoacids.[14,15] This is somewhat strange since α-ureidoacids are stable and readily accessible by reactions of amino acids with KCNO.[14] It is possible that this is due to the influence of the glycolurile fragment.

The formation of target compounds **4** as the main products showed that the reactivity of α- and ω-ureide fragments in α,ω-ureidoacids **1** differs considerably. Cyclisation of the α-ureide fragment to give the hydantoin moiety turned out to be much more favourable than its reaction with 4,5-dihydroxyimidazolidin-2-ones **2**. On the other hand, the ω-fragment was more reactive in the ureidoalkylation with 4,5-dihydroxyimidazolidin-2-ones **2** to give the glycolurile fragment of compounds **4**.

Thus, we found conditions for the synthesis of glycolurile-α-amino acid **8** and performed the one-pot double cyclisation to give hitherto unknown *N*-hydantoinoalkylglycoluriles **4a**,**b** containing three asymmetric centres. Furthermore, the reactivity of the α- and ω-urea fragments of diureidoacids for 4,5-dihydroxyimidazolidin-2-ones differs considerably.

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