Spontaneous resolution in the imidazolidin-2-one series

Angelina N. Kravchenko,*[a] Gul'nara K. Kadorkina,[b] Andrey S. Sigachev,[a] Elena Yu. Maksareva,[a] Konstantin A. Lyssenko,[c] Pavel A. Belyakov,[a] Oleg V. Lebedev,[a] Oleg N. Kharybin,[d] Nina N. Makhova[a] and Remir G. Kostyanovsky[b]

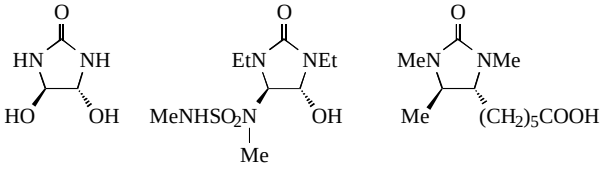
[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 135 5328; e-mail: kani@ioc.ac.ru*
[b] *N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 938 2156; e-mail: kost@chph.ras.ru*
[c] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 135 5085; e-mail: kostya@xrlab.ineos.ac.ru*
[d] *Institute of Energy Problems of Chemical Physics, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 137 8258; e-mail: olmon@chph.ras.ru*

10.1070/MC2003v013n03ABEH001736

For the first time, spontaneous resolution of *trans*-dihydroxyimidazolidin-2-one **1a** was performed and racemisation of (–)-**1a** was studied; regiospecific reaction of **1a**–**c** with aminoguanidine resulted in derivatives **2a**–**c**; compound **2b** was also shown to undergo spontaneous resolution, and the absolute configuration (4*R*,5*R*) of (–)-**2b** crystals was established by X-ray diffraction analysis.

trans-4,5-Dihydroxyimidazolidin-2-one **1a** and its N-alkyl substituted derivatives are intermediates in the synthesis of glycoluriles,[1,2] which are important synthons for preparing molecular capsules[3] and physiologically active compounds.[4]

It was found that racemate **1a**,[1] its derivatives **A**,[2(*i*)] **B**[2(*k*)] (Scheme 1) and a number of glycoluriles[3] crystallise as conglomerates. This property was used for obtaining the chiral drug Albicar (2,6-diethyl-4,8-dimethylglycolurile) through the spontaneous resolution of its synthetic precursor, a 2,6-diethyl derivative,[4(*a*)] followed by dimethylation.[4(*c*)] Both of the enantiomeric forms of Albicar were obtained, and their absolute configurations were established.[4(*c*)]



1a (space group $P2_12_12_1$, $Z = 4$)[1]

A (space group $P2_12_12_1$, $Z = 4$)[2(*i*)]

B (space group $P2_12_12_1$, $Z = 19$)[2(*k*)]

Scheme 1 Conglomerates of imidazolidin-2-ones.

In this work, 4,5-dihydroxyimidazolidin-2-ones (±)-**1a**–**c** were studied. Compound (±)-**1a** forms a conglomerate[1] and easily undergoes the *cis* ⇌ *trans* isomerization owing to the reversible dissociation of the C–O bond. The *trans* isomer was predominant in an equilibrium.

The crystallization of compound (±)-**1a** from water gives large well-shaped crystals possessing optical activity in solution.† The rate of racemization of (–)-**1a** ($\tau_{0.5}$ ~ 4 days at 20 °C in H_2O, $\Delta G^{\neq}$ = 24.8 kcal mol^{-1}) is ideal for the absolute asymmetric synthesis. It allowed us to initiate rapid enantiomerization in solution on heating slightly and to determine the enantiomeric enrichment of the sample after crystallization under normal conditions.[5] However, the exhaustive evaporation of an aqueous solution of (±)-**1a** at 100 °C resulted in the decomposition of the sample (according to ^{1}H NMR spectra). The exhaustive crystallization of an oversaturated solution with the complete self-evaporation of water at 20 °C gives a racemic precipitate (the absence of decomposition was controlled by measuring the ^{1}H NMR and mass spectra). This result can be explained by systematic twinning in the crystallization of (±)-**1a** [*cf.* ref. 4(*b*)], which was supported by a significant scatter of the enantiomeric enrichment of separate crystals obtained by crystallization under usual conditions (Table 1).

Table 1 The optical rotation of individual crystals obtained by crystallization of (±)-**1a** from water.

No.	Mass of crystal/mg	$[a]_\lambda^{20}$ / °				Concentration in H_2O (%)
		578 nm	546 nm	436 nm	406 nm	
1	30.0	–5.3	–7.3	–12.0	–14.7	0.7
2	6.0	+8.2	+9.3	+19.8	+23.3	0.8
3	18.0	–11.0	–12.8	–21.4	–25.4	0.4
4	4.0	–28.0	–31.5	–57.7	–73.5	0.6
5	5.7	+31.9	+34.4	+65.1	+76.1	0.8
6	58.0	–41.0	–45.9	–79.7	–96.6	0.8
7[a]	58.0	–41.3	–48.3	–88.1	–106.2	0.4
8	4.0	–45.5	–50.7	–91.0	–112.0	0.6

[a]Mp 154–158 °C.

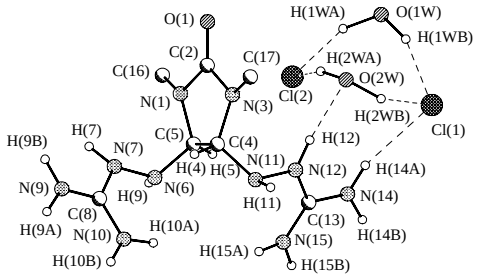
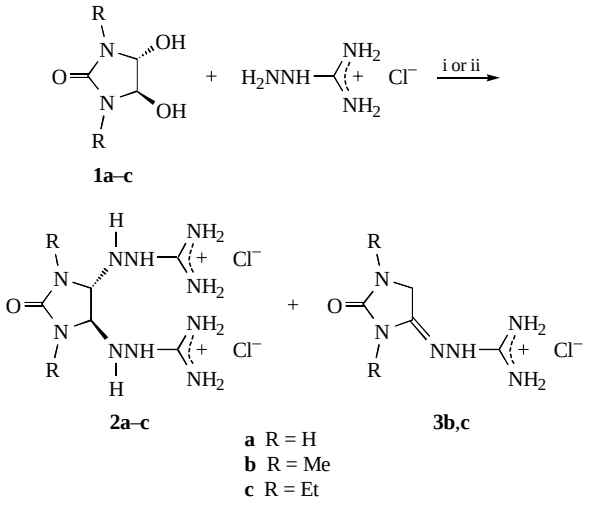


Figure 1 The molecular structure of compound **2b**. Main bond lengths (Å): O(1)–C(2) 1.218(5), N(1)–C(2) 1.381(8), N(1)–C(5) 1.463(6), C(2)–N(3) 1.374(8), N(3)–C(4) 1.455(6), C(4)–N(11) 1.452(6), C(4)–C(5) 1.545(5), C(5)–N(6) 1.430(6), N(6)–N(7) 1.402(7), N(7)–C(8) 1.346(6), C(8)–N(9) 1.313(7), C(8)–N(10) 1.323(7), N(11)–N(12) 1.384(6), N(12)–C(13) 1.340(6), C(13)–N(15) 1.320(7), C(13)–N(14) 1.340(7); valence angles (°): C(2)–N(1)–C(5) 110.4(4), C(2)–N(1)–C(16) 121.5(4), C(5)–N(1)–C(16) 121.0(4), O(1)–C(2)–N(3) 126.2(6), O(1)–C(2)–N(1) 125.2(6), N(3)–C(2)–N(1) 108.6(3), C(2)–N(3)–C(4) 110.6(4), C(2)–N(3)–C(17) 121.0(4), C(4)–N(3)–C(17) 120.9(4), N(11)–C(4)–N(3) 115.3(4), N(11)–C(4)–C(5) 111.7(4), N(3)–C(4)–C(5) 102.5(4), N(6)–C(5)–N(1) 115.7(4), N(6)–C(5)–C(4) 112.4(4), N(1)–C(5)–C(4) 101.9(4), N(7)–N(6)–C(5) 115.1(4), C(8)–N(7)–N(6) 118.6(4), N(9)–C(8)–N(10) 121.6(4), N(9)–C(8)–N(7) 119.7(5), N(10)–C(8)–N(7) 118.7(5), N(12)–N(11)–C(4) 115.1(4), C(13)–N(12)–N(11) 118.3(4), N(15)–C(13)–N(14) 121.4(4), N(15)–C(13)–N(12) 119.5(5), N(14)–C(13)–N(12) 119.1(5).

Reactions of compounds (±)-**1a**–**c**, which were prepared by known methods,[2,4] with aminoguanidine hydrochloride resulted in new derivatives (±)-**2a**–**c** along with by-products **3b**,**c** [*cf.* ref. 4(*b*)], which were characterised by spectroscopic data† (Scheme 2).

The crystallization of **2b** from water allowed us to prepare crystals† suitable for an X-ray study, which showed that this compound crystallised together with two water molecules as a conglomerate (space group $P6_1$, $Z = 6$) (Figure 1).‡ The crystal studied exhibited an optical activity and had a negative sign of



Scheme 2 *Reagents and conditions*: i, H_2O, pH 1–2, 80 °C, 1 h; ii, MeOH, conc. HCl, 60 °C, 1 h.

† NMR spectra were recorded on Bruker WM-400 (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) and Bruker AM-300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) spectrometers. Chemical shifts were measured with reference to residual protons of a [$^2H_6$]DMSO solvent (δ 2.50 ppm). Mass spectra were measured on an MS 30 spectrometer. FT-ICR mass spectra were recorded using a Spectrospin AG CMS-47 instrument and electrospray ionization from solution of (±)-**1a** in H_2O/MeOH (1:1) at a concentration of 10^{-2} mol dm^{-3}. Optical rotation was measured on a Polamat-A polarimeter.

All new compounds gave satisfactory elemental analysis data.

(±)-**1a** was synthesised by the condensation of urea with glyoxal in a basic medium,[1,2(*a*)] mp 140 °C [lit. data, mp 133–135 °C (from H_2O/EtOH at –12 to –20 °C),[2(*b*)] mp 140 °C (from MeOH–H_2O, 2:3),[1] mp 141–142 °C (from H_2O)[2(*c*)] and mp 146 °C (from MeOH)[2(*a*)]].

For individual crystal of (–)-**1a**, $[\alpha]_{578}^{20}$ –41.3 (*c* 0.4, H_2O), mp 154–158 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.56 (d, 2H, 2CH, ^3J 6.0 Hz), 5.85 (d, 2H, 2OH, ^3J 6.0 Hz), 7.06 {br. s, 2H, 2NH [*cf.* refs. 1,2(*b*)]}. ^{13}C NMR ([$^2H_6$]DMSO) δ: 84.0 (d, CH, ^1J 161.1 Hz), 160 (s, CO). MS ICR (±)-**1a**, *m*/*z* (*I*, %): 119 (1) [M + H]$^+$, 141 (100) [M + Na]$^+$, 237 (5) [2M + H]$^+$, 259 (3) [2M + Na]$^+$, 377 (1) [3M + Na]$^+$.

The crystallization of 300 mg (±)-**1a** from a dilute aqueous solution for a week at 20 °C resulted in a precipitate, from which well-shaped optically active crystals were selected (183.7 mg) (Table 1).

4,5-bis(3-Aminoguanidino)imidazolidin-2-one dihydrochloride **2a**: 68% yield, mp 230–231 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.21 (s, 2H, 2CH), 5.89 (br. s, 2H, 2NH), 6.89 (s, 2H, NH–CO–NH), 7.00–7.85 (br. m, 8H, 2NH$_2^+$, 2NH$_2$), 9.02 (br. s, 2H, 2NH).

1,3-Dimethyl-4,5-bis(3-aminoguanidino)imidazolidin-2-one dihydrochloride **2b**: 57% yield, mp 222–224 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.67 (s, 6H, 2Me), 3.98 (s, 2H, 2CH), 6.32 (s, 2H, 2NH), 6.85–7.98 (br. m, 8H, 2NH$_2^+$, 2NH$_2$), 9.08 (s, 2H, 2NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 28.4 (2Me), 73.3 (2CH), 158.4 (C=O), 159.4 (C=NH$_2^+$).

Two kinds of crystals (hexagonal and rhombic plates) possessing optical activity were prepared by crystallization of (±)-**2b** from water with self-evaporation.

For a rhombic crystal, $[\alpha]_D^{20}$ +5.8 (*c* 1.7, 0.1 N HCl).

The second kind of hexagonal crystals was divided into two parts. For a greater part $[\alpha]_D^{20}$ –8.6 (*c* 2.0, 0.1 N HCl). A smaller part was used for X-ray diffraction analysis to determine‡ the absolute configuration (4*R*,5*R*)-(–)-**2b**.

1,3-Diethyl-4,5-bis(3-aminoguanidino)imidazolidin-2-one dihydrochloride **2c**: 49% yield, mp 213–214 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.94 (t, 6H, 2Me, ^3J 6.7 Hz), 3.05 (m, 2H, CH$_2$), 3.32 (m, 2H, CH$_2$), 4.10 (s, 2H, 2CH), 6.29 (s, 2H, 2NH), 6.87–7.95 (br. m, 8H, 2NH$_2^+$, 2NH$_2$), 8.89 (s, 2H, 2NH). MS, *m*/*z* (*I*, %): 212 (90) [M$^+$ – NH$_2$NHC(NH)NH$_2$], 180 (12), 168 (25), 155 (26), 153 (28), 141 (50), 140 (63), 116 (63), 114 (47), 98 (85), 97 (56), 69 (63), 58 (81), 56 (100).

4-Guanidinimino-1,3-dimethylimidazolidin-2-one dihydrochloride **3b**: 32% yield, mp 227–228 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.85 (c, 3H, N–Me), 2.96 (c, 3H, N–Me), 4.25 (c, 2H, CH$_2$), 7.40 (br. s, 4H, NH$_3^+$, NH), 11.05 (s, 1H, NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 26.1 (Me), 29.7 (Me), 47.8 (CH$_2$), 151.7 (C=O), 155.7 (C=N), 156.6 (C=N).

4-Guanidinimino-1,3-diethylimidazolidin-2-one dihydrochloride **3c**: 30% yield, mp 205–206 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.05 (m, 6H, 2C–Me), 3.07 (m, 4H, N–CH$_2$), 4.25 (s, 2H, CH$_2$), 7.50 (br. s, 4H, NH$_2$ + NH$_2^+$), 11.00 (s, 1H, NH).

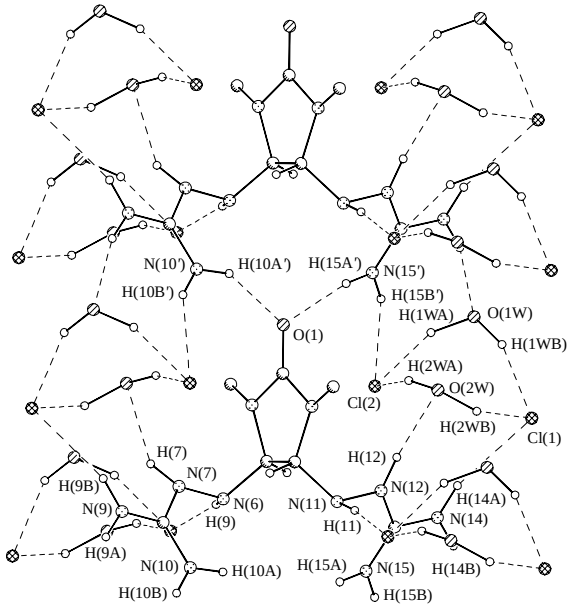


Figure 2 Schematic diagram of a homochiral H-bonded chain along the axis *a* in the crystal structure of compound **2b**. The parameters of H-bonds: OH···Cl [O···Cl 3.056(7)–3.232(7) Å, H···Cl 2.09–2.30 Å, OHCl 134–157°], N–H···O [N···O 2.799(7)–2.937(7) Å, H···O 1.93–2.01 Å, NHO 142–165°], N–H···Cl [N···Cl 3.286(7)–3.418(7) Å, H···Cl 2.42–2.57 Å, NHCl 154–167°].

optical rotation. Therefore, the absolute configuration of this compound was established as (4*R*,5*R*)-(–)-**2b**.†

The molecular structure of **2b** is characterised by the conformation of a five-membered ring as a flat envelope with the deviation of the C(5) atom by 0.36 Å; aminoguanidinium substituents exhibit a *trans* arrangement [the N(6)C(5)C(4)N(1) torsion angle is 88°]. Their geometry is almost identical to the structure of aminoguanidinium anions in chloride and nitrate salts.[6] The bond lengths in C(NH$_2$)$_2^+$ fragments are equalised [1.313(7)–1.347(7) Å]. It is likely that insignificant variations are due to differences in the number and strength of H-bonds with the participation of all H atoms of these groups.

The supramolecular structure of compound **2b** is unusual. The molecules in a crystal are joined by N–H···O bonds into homochiral translation chains oriented along the axes *a* and *b* (Figure 2). These symmetrically equivalent mutually perpendicular chains are 'framed' by eight-membered H-bonded rings formed by solvation water molecules and chloride anions due to N–H···O and N–H···Cl bonds. These eight-membered rings join the chains into a three-dimensional homochiral framework.

‡ *Crystallographic data for* **2b**: at 110 K, the crystals of $C_7H_{24}Cl_2N_{10}O_3$ are hexagonal, space group $P6_1$, a = 7.447(1) Å, c = 52.90(1) Å, V = = 2540.7(9) Å^3, Z = 6, M = 367.26, d_{calc} = 1.440 g cm^{-3}, μ(MoKα) = = 4.12 cm^{-1}, F(000) = 1164. Intensities of 15095 reflections were measured with a Smart 1000 CCD diffractometer at 110 K [λ(MoKα) = 0.71072 Å, ω-scans with a 0.3° step in ω and 15 s per frame exposure, $2\theta < 55°$], and 3519 independent reflections (R_{int} = 0.0445) were used in a 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. Hydrogen atoms were located from the Fourier synthesis and refined in the 'riding model' approximation. The absolute configuration was estimated based on the Flack parameter, which was 0.0(1) for the *R* configuration of C(4) and C(5) atoms. The refinement converged to wR_2 = 0.1927 and GOF = 1.089 for all independent reflections [R_1 = 0.0685 was calculated against F for 2839 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0 on IBM PC AT.

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 214874. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2003.

This work was supported by INTAS (grant no. 99-0157), the Russian Foundation for Basic Research (grant nos. 02-03-33257, 03-03-32019, 03-03-06532 and 00-03-81187Bel) and the Russian Academy of Sciences.

References

1 E. Grillon, R. Gallo, M. Pierrot, J. Boileau and E. Wimmer, *Tetrahedron Lett.*, 1988, **29**, 1015.

2 (*a*) H. Pauly and H. Sauter, *Ber.*, 1930, **63B**, 2063; (*b*) S. L. Vail, R. H. Barker and P. G. Mennitt, *J. Org. Chem.*, 1965, **30**, 2179; (*c*) H. E. Zaagg, and W. B. Martin, *Organic Reactions*, John Wiley, New York, 1965, vol. 14, p. 52; (*d*) H. Peterson, *Leibigs Ann. Chem*., 1969, **726**, 89; (*e*) S. Gautman, R. Ketcham and J. Nematollahi, *Synth. Commun*., 1979, **9**, 863; (*f*) A. R. Butler and E. Leitch, *J. Chem. Soc*., *Perkin Trans. 2*, 1980, 103; (*g*) A. N. Kravchenko, O. V. Lebedev and Yu. Maksareva, *Mendeleev Commun*., 2000, 27; (*h*) K. Yu. Chegaev, A. N. Kravchenko, O. V. Lebedev and Yu. A. Strelenko, *Mendeleev Commun.*, 2001, 32; (*i*) G. A. Gazieva, K. A. Lyssenko, R. G. Gaziev, A. N. Kravchenko, O. V. Lebedev and V. M. Zhulin, *Mendeleev Commun*., 2001, 107; (*j*) G. A. Gazieva, A. N. Kravchenko, O. V. Lebedev, K. A. Lyssenko, M. O. Dekaprilevich, V. M. Men'shov, Yu. A. Strelenko and N. N. Makhova, *Mendeleev Commun*., 2001, 138; (*k*) N. Okabe and Y. Sasaki, *Chem. Pharm. Bull*., 1994, **42**, 2143.

3 (*a*) F. Hof, S. L. Craig, C. Nuckolls and J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl*., 2002, **41**, 1488; (*b*) A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc*., 2002, **124**, 12074.

4 (*a*) R. G. Kostyanovsky, K. A. Lyssenko, G. K. Kadorkina, O. V. Lebedev, A. N. Kravchenko, I. I. Chervin and V. R. Kostyanovsky, *Mendeleev Commun.*, 1998, 231; (*b*) R. G. Kostyanovsky, K. A. Lyssenko, A. N. Kravchenko, O. V. Lebedev, G. K. Kadorkina and V. R. Kostyanovsky, *Mendeleev Commun*., 2001, 134; (*c*) R. G. Kostyanovsky, G. K. Kadorkina, K. A. Lyssenko, V. Yu. Torbeev, A. N. Kravchenko, O. V. Lebedev, G. V. Grinselev-Knyazev and V. R. Kostyanovsky, *Mendeleev Commun*., 2002, 6.

5 R. G. Kostyanovsky, V. R. Kostyanovsky, G. K. Kadorkina and K. A. Lyssenko, *Mendeleev Commun*., 2001, 1.

6 A. Aekella and D. A. Koszler, *Acta Crystallogr.*, 1974, **C50**, 1994.

Received: 4th March 2003; Com. 03/2062