3-Hydroxy-2,2-dimethylimidazolidin-4-one: the regioselective synthesis and chiral crystallization

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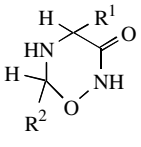
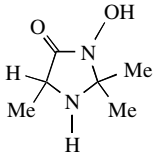
The condensation of glycine hydroxamic acid with acetone regioselectively leads to the formation of the title achiral cyclic hydroxamic acid, which crystallises from an acetone solution as chiral crystals (space group $P2_12_12_1$) of (*P*,1*R*,3*S*) and (*M*,1*S*,3*R*) enantiomers.

Alkylation and acylation of unsubstituted hydroxamic acids (HA) mainly lead to their (N)-O derivatives.[1] For example, the reaction of α-amino HA with aldehydes affords cyclic *O*-alkyl hydroxamates **1** or corresponding acyclic azomethins.[2]

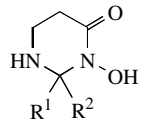
Nevertheless, it was found previously[3] that the condensation of DL-α-alanine hydroxamic acid (α-AlaHA) with acetone proceeds as the regioselective N-alkylation of the hydroxamic group to provide cyclic HA **2** in 83% yield. This finding is in agreement with the reactions of β-AlaHA with aliphatic aldehydes or ketones solely giving products **3**.[4]



1 R^1, R^2 = Alk, Ar

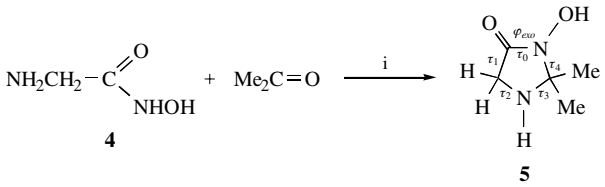


(±)-**2**



3 R^1, R^2 = H, Alk

In this work, we report that the condensation of glycine HA (GlyHA **4**) with acetone proceeds similarly[3] to afford cyclic HA **5** (Scheme 1).



Scheme 1 *Reagents and conditions*: i, suspension of 450 mg (5 mmol) of GlyHA, acetone (2 equiv.) and 50 cm^3 of MeOH, reflux, 3 h, then filtration, evaporation, and recrystallization from acetone.

The structure of product **5** was found by X-ray diffraction analysis† and confirmed by spectroscopic data‡ and the test reaction with $FeCl_3$.

According to ^{1}H and ^{13}C NMR spectra,‡ neither the ring–chain tautomerism nor the hydroxyamide–hydroxynitrone tautomerism (O=C–N–OH ⟷ HO–C=N→O) of the chelate type, which are slow and fast,[5(a)] on an NMR time scale, respectively, have been observed for **5** in solution. The absence of the hydroxyamide–hydroxynitrone tautomerism follows from the comparison of the chemical shifts of carbonyl carbons for **5** (δ 171.8 ppm)‡ and 3-methoxy-1,2,2,5,5-pentamethylimidazolidin-4-one **6** (δ 171.1 ppm, in MeOH),[5(b)] bearing in mind that **6** has no ability for such a kind of tautomerism. The significant upfield shift of the methoxyimine carbon signal (δ 156.7 ppm, in MeOH) of a methoxynitrone derivative of **6** (MeO–C=N→O)[5(b)] supports this conclusion.

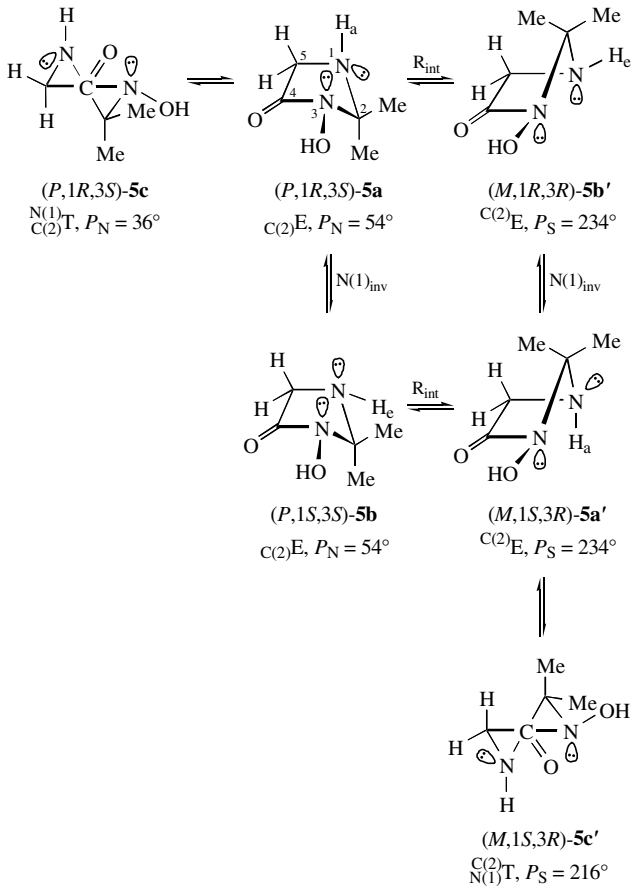
The characteristic feature of the molecular structure of **5** in a crystal (Figure 1) is the non-planarity of the hydroxamic fragment O=C–N–O (φ_{exo} = 19.3°), which is caused probably by the minimization of the dipole–dipole repulsion of its *cis*-oriented dipoles and torsion strain of exocyclic C=O and N–O bonds. The synperiplanar (*sp*) twist of a hydroxamic fragment specifies the spiral chirality as *P* (plus, $\varphi_{exo} > 0$) (Figure 1) or *M* (minus, $\varphi_{exo} < 0$),[6] depending on the heterocycle conformation chirality (*vide infra*) of the molecule of **5**, and it is inconsistent with the general point of view[1] concerning the planarity of a hydroxamic fragment in HAs. Thus, in the molecule of **5**, the displacements of O(1), N(1) and C(2) atoms from the mean plane N(3)C(4)C(5)O(2) (to within ±0.0005 Å) are equal to 0.396, –0.126 and 0.348 Å, respectively.

An opposite sence of twist of exo- (φ_{exo}) and endocyclic (τ_0) dihedral angles at the central N(3)–C(4) amide bond, as well as the presence of the electronegative O(1) substituent adjacent to the N(3) atom, promote[7] the weakening of the n_N–π*(C=O) amide resonance and an increase in the sp^3 character and pyramidalization of the amide N(3) atom [Σω N(3) = 350.8°; the height of the pyramid is equal to 0.25 Å]. Correspondingly, a lengthening of the N(3)–C(4) bond and a shortening of the C(4)=O(2) bond are observed in **5** (Figure 1) as compared with the average lenghts of the corresponding bonds [N–C(O),

† *Crystallographic data for* **5** at 120 K: crystals of $C_5H_{10}N_2O_2$ are orthorhombic, space group $P2_12_12_1$, a = 7.1099(9), b = 9.4282(11) and c = 9.7646(10) Å, V = 654.56(13) Å^3, Z = 4, M = 130.15, d_{calc} = 1.321 g cm^{-3}, μ(MoKα) = 0.103 mm^{-1}, F(000) = 280. Intensities of 2438 reflections were measured with a Smart 1000 CCD diffractometer at 120 K [λ(MoKa) = = 0.71073 Å, ω-scans with a 0.3° step in ω and 10 s per frame exposure, $\theta < 27°$], and 1297 independent reflections (R_{int} = 0.0299) were used in 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 isotropic approximation. The refinement converged to wR_2 = 0.1412 and GOF = 0.973 for all independent reflections [R_1 = 0.0532 was calculated against F for 1040 observed reflections with $I > 2\sigma(I)$]. The number of the refined parameters was 122. 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). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2002. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/109.

‡ *Characteristics and spectroscopic data*. IR spectra were obtained on a Specord-82M spectrometer. NMR spectra were recorded on a Bruker WM-400 NMR spectrometer (with TMS as an internal standard) at 400.13 (^{1}H) and 100.62 MHz (^{13}C). Compound **4** (GlyHA) was prepared as described previously.[17]

5: yield 57%, mp 177–178 °C (decomp.). ^{1}H NMR (CD_3OD) δ: 1.37 (s, 6H, 2Me), 3.37 (s, 2H, CH_2). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.19 (s, 6H, 2Me), 3.12 (br. s, 1H, NH), 3.14 (s, 2H, CH_2), 9.39 (br. s, 1H, OH). ^{13}C NMR (CD_3OD) δ: 24.24 (qq, Me, ^1J 127.4 Hz, ^3J 3.1 Hz), 45.88 (tr, CH_2, ^1J 143.8 Hz), 78.80 (m, NCN), 171.80 (tr, C=O, ^2J 5.0 Hz). IR (KBr, ν/cm^{-1}): 3214 (NH), 2982, 2928 (Me, CH_2), 2719 (br.), 2631 (br.), 2538 (br., OH), 1697 (C=O), 1514, 1472, 1464, 1389, 1368, 1308, 1256, 1180, 1170, 1112, 1081, 1040, 1001, 968, 945 sh, 933, 900, 838, 705, 610, 579, 532, 412.



Scheme 2 Degenerate racemization of **5** as illustrated by ideal molecular shapes.

1.335(1) Å; C=O, 1.232(1) Å][8(a)] of γ-lactams in a crystalline state.

According to the quantitative evaluation of the heterocyclic ring form of **5** in a crystal (Figure 1) based on the pseudorotation parameters such as phase angle (*P*) and amplitude of puckering (τ_m),[9] the chiral N-type ($\tau_2 > 0$) conformation of the heterocyclic ring of **5** (P_N = 44.4°, τ_m = 31.4°) is intermediate between the forms of ideal half-chair $^{N(1)}_{C(2)}$T (P_N = 36°, $\tau_0 = \tau_1$, $\tau_2 = \tau_4$, $\tau_3 = \tau_{max}$) and envelope $_{C(2)}$E (P_N = 54°, $|\tau_0| = \tau_2$, $|\tau_3| = \tau_4$, $\tau_1 = 0$), the latter form being typical of imidazolidines.[10] The phase angles P_S for corresponding enantiomeric forms $^{C(2)}_{N(1)}$T and $_{C(2)}$E of S-type ($\tau_2 < 0$) heterocycle will be equal to 216° and 234° (Scheme 2), respectively.

The pyramidality of the amine N(1) atom [Σω N(1) = 317.2°] is enhanced by its inclusion into a heterocyclic ring and by a compression of the endocyclic C(2)N(1)C(5) bond angle. This corresponds to an increase in the *p*-character of hybrid orbitals of the N(1) atom in 'internal' N(1)–C(2) and N(1)–C(5) bonds, leading to an elongation of these bonds (Figure 1) in comparison with the averaged X-ray diffraction value (1.469 Å)[8(b)] for the $(C)_2$–Nsp^3 bond.

The pseudo-*e* orientation of the N(1) lone pair (LP) assists the $n_{N(1)}$–$\sigma^*_{C(2)–N(3)}$ interaction (anomeric effect[7]) caused by the antiperiplanar (*ap*) orientation of this LP to the C(2)–N(3) bond [φ $LP_{N(1)}$N(1)C(2)N(3) = –152.5°]. Together with the concerted $n_{O(1)}$–$\sigma^*_{N(3)–C(2)}$ interaction [φ $LP_{O(1)}$O(1)N(3)C(2) = –145°], this results in an appreciable weakening of the C(2)–N(3) bond in **5** (Figure 1) as compared to the mean X-ray diffraction length [1.455(1) Å][8(a)] of the N–$C_β$ bond in γ-lactams.

Moreover, the pseudo-*e* $LP_{N(1)}$ has the *ap*-orientation to $LP_{N(3)}$ [pseudo-dihedral angle φ $LP_{N(1)}$N(1)N(3)$LP_{N(3)}$ = 154°, and the bond angle between these LP vectors is equal to 122°], which promotes the decreasing of their dipole–dipole repulsion (*cf.* μ_D for **5a** and **5b**, *vide infra*) and corresponds to a preferable mutual orientation of the LPs of the NCN geminal system.[11]

The heterocycle conformation of **5** in a crystal is also stabilised by *ap*-orientation as of N(1)–C(2) and N(3)–O(1) polar bonds [φ N(1)C(2)N(3)O(1) = 175.2(2)°], and also of N(1)–C(5) and C(4)=O(2) bonds [φ N(1)C(5)C(4)O(2) = 174.9(2)°], which assist the diminution of their dipole–dipole repulsion and torsion strain.

The enhancement of the directivity of pseudo-*e* oriented $LP_{N(1)}$ increases the proton-accepting ability of the N(1) atom and aids to the forming of the strong O(1)–H(1O)···N(1) intermolecular H-bond of the zwitterionic type. Another type of intermolecular H-bonding observed in the crystal of **5** is a weak[12] H-bond of the N(1)–H(1)···O(2)=C(4) type (Figure 2).

The comparison of homologues **2** and **5** demonstrates that their molecular structures in a crystalline state are conformationally similar [*cf.* P_N = 39.5°, τ_m = 35.5°, Σω N(3) = 351.2° for **2**].[3] Nevertheless, their crystal structures formed by the same types of intermolecular H-bonds are essentially distinct from each other. Thus, configurationally rigid racemate **2** crystallises from an acetone solution as heterochiral crystals (space group $P2_1/c$, $Z = 8$, mp 163–164 °C),[3] whereas non-rigid (formally achiral) HA **5** gives chiral crystals (space group $P2_12_12_1$, $Z = 4$, mp 177–178 °C)† from this solvent.

According to the geometry and energy of **5** optimization by the DFT method (Becke3LYP/6-31G*),§ the dominant conformer **5a** [for (*P*,1*R*,3*S*) enantiomer] is stabilised in an isolated state in a quite ideal $_{C(2)}$E envelope form of the heterocyclic ring (P_N = 53.8°, τ_m = 32.8°) with the retention of a noticeable twist

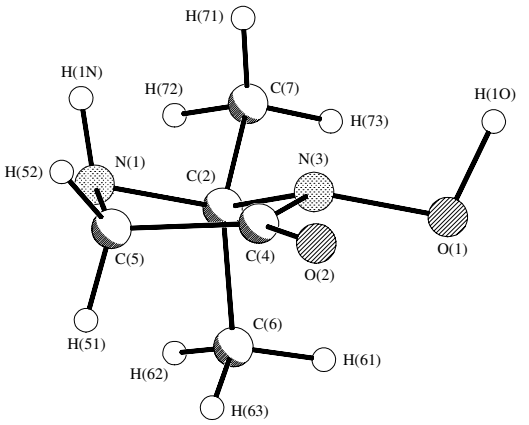


Figure 1 Molecular structure of hydroxamic acid **5**. [The absolute configuration is not known, and our assignment as (*P*,1*R*,3*S*) is only illustrative]. Selected bond lengths (Å): O(1)–N(3) 1.394(3), N(1)–C(2) 1.475(3), N(1)–C(5) 1.489(4), O(2)–C(4) 1.225(3), C(2)–N(3) 1.484(3), C(2)–C(6) 1.523(4), C(2)–C(7) 1.523(4), N(3)–C(4) 1.343(3), C(4)–C(5) 1.512(4); selected bond and dihedral angles (°): C(2)–N(1)–C(5) 106.1(2), N(1)–C(2)–N(3) 100.4(2), N(1)–C(2)–C(6) 112.1(2), N(1)–C(2)–C(7) 110.8(2), N(3)–C(2)–C(6) 109.9(2), N(3)–C(2)–C(7) 111.4(2), C(6)–C(2)–C(7) 111.8(2), O(1)–N(3)–C(2) 117.7(2), O(1)–N(3)–C(4) 119.7(2), C(2)–N(3)–C(4) 113.4(2), O(2)–C(4)–N(3) 127.1(2), O(2)–C(4)–C(5) 127.4(2), N(3)–C(4)–C(5) 105.6(2), N(1)–C(5)–C(4) 105.3(2); H(1O)–O(1)–N(3)–C(2) 95, H(1O)–O(1)–N(3)–C(4) –120, H(1N)–N(1)–C(2)–N(3) 82.3, C(5)–N(1)–C(2)–N(3) (τ_3) –29.3(2), C(5)–N(1)–C(2)–C(6) 87.2(3), C(5)–N(1)–C(2)–C(7) –147.1(2), H(1N)–N(1)–C(5)–H(51) 153.4, H(1N)–N(1)–C(5)–H(52) 29.3, C(2)–N(1)–C(5)–C(4) (τ_2) 22.4(3), N(1)–C(2)–N(3)–C(4) (τ_4) 28.4(3), C(6)–C(2)–N(3)–O(1) 57.0(3), C(6)–C(2)–N(3)–C(4) –89.8(3), C(7)–C(2)–N(3)–O(1) –67.5(3), C(7)–C(2)–N(3)–C(4) 145.7(2), O(1)–N(3)–C(4)–O(2) (φ_{exo}) 19.3(4), O(1)–N(3)–C(4)–C(5) –160.9(2), C(2)–N(3)–C(4)–O(2) 165.3(2), C(2)–N(3)–C(4)–C(5) (τ_0) –14.9(3), N(3)–C(4)–C(5)–N(1) (τ_1) –5.0(3).

§ The geometries of cyclic hydroxamic acid (*P*,1*R*,3*S*)-**5a** and its diastereomer (*P*,1*S*,3*S*)-**5b** were completely optimised at the density functional theoretical level (DFT) with the conventional 6-31G* basis set using procedures implemented in the Gaussian 98 system of programs.[18] For the DFT calculations, a hybrid approach based on Becke's three parameter functional[19] was employed (Becke3LYP). As the convergence criteria the default threshold limits of 0.00045 and 0.0018 a.u. were applied for the maximum force and displacement, respectively. The calculated energies (in hartrees) and dipole moments (in debyes) are: –456.45047 and 2.54 (**5a**), –456.44352 and 3.35 (**5b**), respectively. We are grateful to Professor Yu. N. Bubnov (Institute of Organoelement Compounds, Russian Academy of Sciences) for his help in carrying out the quantum-chemical calculations.

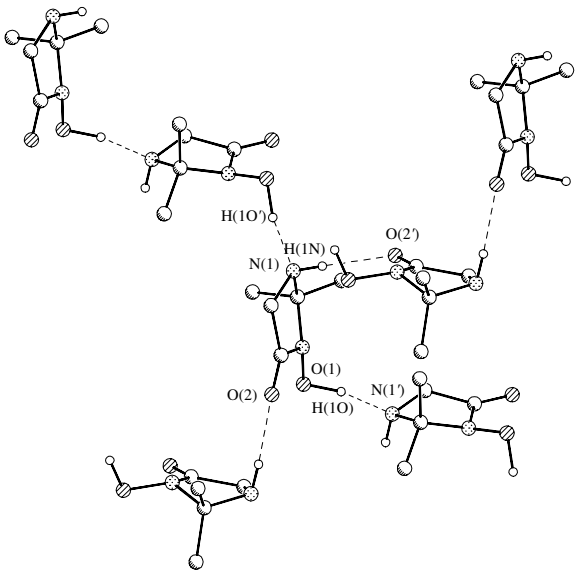


Figure 2 Hydrogen-bonded helixes in the crystal structure of **5** (perspective view on the *bc* plane). Hydrogen bonds are shown by dashed lines. The geometric parameters of H-bonds are as follows: H(1O)···N(1) 1.599 Å, O(1)···N(1) 2.679 Å, O(1)–H(1O)···N(1) 167.9°; H(1N)···O(2) 2.155 Å, N(1)···O(2) 3.041 Å, N(1)–H(1N)···O(2) 174.4°. [The symmetry transformations used to generate the atoms N(1) ($-x-1/2$, $-y+1$, $z+1/2$) and O(2) ($-x$, $y-1/2$, $-z+1/2$)].

of the hydroxamic fragment of the same spirality sence (*P*, $\varphi_{exo} = 16.1°$), a slight pyramidality of amide N(3) nitrogen [$\Sigma\omega$ N(3) = 346.6°], and the pseudo-*e* orientation of $LP_{N(1)}$ [φ H(1N)N(1)C(2)N(3) = 86.5°] of the pyramidal N(1) atom [$\Sigma\omega$ N(1) = 322.9°] with (*R*)-configuration. However, its N(1) epimer [(*P*,1*S*,3*S*) diastereomer **5b**, Scheme 2] with the pseudo-*a* orientation of $LP_{N(1)}$ [φ H(1N)N(1)C(2)N(3) = –152.9°], having the same handedness (N-type, $\tau_2 = 22.2°$) of heterocycle conformation, exhibits the structure [$P_N = 45.5°$, $\tau_m = 31.7°$, φ_{exo} = = 22.1°, $\Sigma\omega$ N(3) = 349.3°, $\Sigma\omega$ N(1) = 331.1°] almost identical to **5** in a crystal, but it is populated by less than 0.1% relatively to **5a** [relative energy $-\Delta E^0_{(\mathbf{5a,b})} = 4.36$ kcal mol^{-1}].§

Steric and stereoelectronic factors, stabilising as the heterocycle conformation in form close to $_{C(2)}$E [or $^{C(2)}$E] envelope and pseudo-*e* orientation of $LP_{N(1)}$ of molecule **5** in crystal (*vide supra*) and free (**5a**) states are probably the same. However, a weak intramolecular H-bond of the O–H···O=C type [*d* H(1O)···O(2) = 2.08 Å, φ_1 H(1O)O(1)N(3)C(4) = –6.4°] exists in **5a**, whereas it is absent from the crystalline state [*d* H(1O)···O(2) = 3.42 Å, $\varphi_1 = -120°$] (Figure 1) and the molecule of **5b** [*d* H(1O)···O(2) = 2.98 Å, $\varphi_1 = -88.6°$]. The absence of this H-bond is sterically favourable for a decrease in the mutual repulsion of $LP_{N(3)}$ and $LP_{[O(1)]}$ {φ $LP_{N(3)}$ N(3)O(1)$LP^1_{O(1)}$ [$LP^2_{O(1)}$] = –132° and 108° in the crystal of **5**}.

Thus, compound **5** is conformationally and tautomerically homogeneous in both a crystal and solution, existing as (*P*,1*R*,3*S*) and (*M*,1*S*,3*R*) enantiomers, for which degenerate racemization probably consists of two relatively independent diastereomeric steps of stereomutation (Scheme 2): (*a*) the interconversion of chiral conformation of heterocycle (from N to S type and *vice versa*) by a pseudorotational or 'through the plane' mechanism,[9(a)] which is accompanied by the concurrent inversion of a shallow pyramid of amide nitrogen N(3) and the reversion of a helix chirality (*P* or *M*) of the hydroxamic fragment and (*b*) the configuration inversion of the amine N(1) atom by its pyramid inversion or proton transfer.

The low energy of activation of the rate-limiting epimerization (either *a* or *b*) of sterically unhindered racemization of **5** did not allow us to observe (in solution) the chemical shift nonequivalence of signals from the geminal prochiral methyl groups or methylene group protons in the NMR spectra‡ at ambient temperature and the optical activity of the enantiomeric form of **5**.

The generation of chiral crystals by the crystallization of configurationally flexible compound **5** proceeds by such a way that the frozen chiral conformations of only one handedness are self-assembled in each single crystal, inducing crystal chirality. Enantiomorphous crystals consist of infinite helixes formed by strong (O–H···N type) and weak (N–H···O=C type) H-bonds along the crystallographic axes *c* and *b*, respectively (Figure 2), leading to the generation of a spatial H-bonded network.

In conclusion, note that chiral crystals obtained from achiral compounds[13] are substrates for absolute asymmetric synthesis[14] and new chiral materials for non-linear optics.[15] Moreover, their generation in the absence of any external chiral agent is interesting both for chiral crystal engineering and for solving the question of the origin of optical activity in nature.[16]

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