General regioselective synthesis of 2,2-disubstituted 3-hydroxyimidazolidin-4-ones

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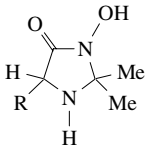
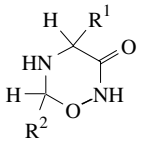
The reactions of glycine hydroxamic acid with aliphatic ketones and acetophenone are commonly used for the regioselective synthesis of cyclic hydroxamic acids 6a–e; spiro hydroxamic acid 6a was structurally characterised by X-ray diffraction analysis.

Hydroxamic acids (HAs) possess a wide spectrum of biological activities,[1(a)] high affinity to transition metals[1(b)] (*e.g.*, naturally occurring hydroxamate siderophores, which are iron(III) chelators)[1(c)] and enzyme inhibition properties (for example, as matrix metalloproteinase inhibitors).[2] This causes current interest in the development of novel synthetic routes and the preparation of novel selective, small hydroxamate peptidomimetics[3(a)] and siderophore analogues.[3(b)]

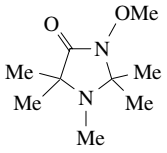
We found previously[4,5] that the reactions of glycine and DL-α-alanine hydroxamic acids with acetone afford cyclic hydroxamic acids **1** and **2**, respectively, *i.e.*, proceed as regioselective intramolecular N-aminoalkylation of the hydroxamic group (CONHOH) of substrates (GlyHA and AlaHA). However, it is known that the condensation of α-amino HAs with aldehydes yields products **3** of intramolecular (N)-O-aminoalkylation or corresponding acyclic azomethins.[6] The preferred (N)-O-alkylation and (N)-O-acylation are also typical of unsubstituted HAs.[7,8]



1 R = H
(±)-**2** R = Me



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



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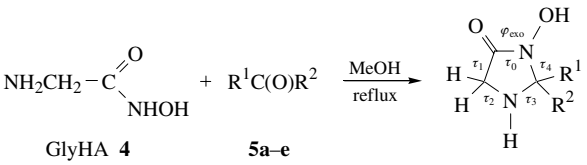
In this work, we found that the reactions of GlyHA **4** with aliphatic ketones **5a–d** and acetophenone **5e** proceed to one way[4,5] as N,N′-cyclocondensation to form 2,2-disubstituted 3-hydroxyimidazolidin-4-ones **6a–e** (Scheme 1). The crystal structure of achiral spiro cyclic HA **6a** was investigated in this work owing to its homologue achiral HA **1** forms enantiomorphous crystals.[4]



GlyHA **4** + **5a–e** → (MeOH, reflux)

6a $R^1 + R^2 = (CH_2)_4$
6b $R^1 + R^2 = (CH_2)_5$
(±)-**6c** R^1 = Me, R^2 = Et
(±)-**6d** R^1 = Me, R^2 = Bu^t
(±)-**6e** R^1 = Me, R^2 = Ph

Scheme 1

The structures of products **6a–e** were confirmed by spectroscopic data† (which are consistent with published data for **1**,**2**[4,5]), the colour test reaction with $FeCl_3$ and X-ray diffraction analysis for **6a**.‡

The only set of resonance signals corresponding to the hydroxyamide (oxo) tautomeric form is observed in the ^1H and ^{13}C NMR spectra† of **6a–e** to give evidence for the absence (> 5%) of other tautomeric forms, namely, acyclic (azomethine) or zwitterionic.

The absence of noticeable hydroxyamide–hydroxynitrone tautomerism (O=C–N–OH ⟷ HO–C=N→O), which is fast on the NMR time scale,[9(a)] in solution for **6a–e** follows from the comparison of chemical shifts for C(4) carbon resonance signals in ^{13}C NMR spectra of **6a–e**† and model compounds, existing as fixed tautomeric forms, namely, methylhydroxamate

† *General procedure for the synthesis of 3-hydroxyimidazolidin-4-ones* **6a–e**. A suspension of GlyHA **4** (0.9 g, 10 mmol) and ketone **5a–e** (12 mmol) in 30 ml of absolute methanol was refluxed for 1–2 h. Then, the reaction mixture was filtered, the solution was evaporated to dryness, and the resulting residue was recrystallised from an appropriate solvent to yield **6a–e** as colourless crystals. In each case, the oily residue evaporated from a waste mother liquor was examined by column chromatography (SiO_2) and ^1H NMR spectroscopy in order to verify the reaction selectivity. Reactant **4** (GlyHA) was prepared as described previously.[21]

Characteristics and spectroscopic data. NMR spectra were recorded on a Bruker WM-400 NMR spectrometer at 400.13 (^1H) and 100.62 MHz (^{13}C). IR spectra were obtained on a Specord-82M spectrometer.

6a: yield 43%, mp 153–154 °C (EtOH). ^1H NMR (CD_3OD) δ: 1.70 (m, 2H, CH_2), 1.74 (m, 4H, $2CH_2$), 2.05 (m, 2H, CH_2), 3.34 (s, 2H, NCH_2). ^1H NMR ([$^2H_6$]DMSO) δ: 1.52 (m, 2H, CH_2), 1.58 (m, 4H, $2CH_2$), 1.82 (m, 2H, CH_2), 3.12 (s, 3H, $NHCH_2$), 9.48 (br. s, 1H, OH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 23.69 (br. t, $2CH_2$, ^1J 130.9 Hz), 33.34 (br. t, $2CH_2$, ^1J 129.5 Hz), 45.52 (td, NCH_2, ^1J 142.1 Hz, $^2J_{NH}$ 9.8 Hz), 86.60 (m, NCN), 170.22 (m, C=O). IR (KBr, ν/cm^{-1}): 3195 (NH), 2964, 2954 2910, 2873 (CH_2), 2716 (br), 2569 (br, OH), 1716 (C=O), 1702 (sh), 1654 (sh), 1556, 1544, 1467, 1436, 1428, 1381, 1332, 1297, 1243, 1217, 1190, 1145, 1101, 1037, 980, 951, 865, 813, 673, 581.

6b: yield 39%, mp 155–156 °C (dioxane). ^1H NMR (CD_3OD) δ: 1.19 (m, 1H, C*H*H), 1.58–1.73 (br. m, 7H, CH_2), 1.82 (m, 2H, CH_2), 3.34 (s, 2H, NCH_2). ^1H NMR ([$^2H_6$]DMSO) δ: 1.04 (m, 1H, CH_2), 1.43–1.63 (br. m, 9H, CH_2), 2.94 (br. s, 1H, NH), 3.12 (s, 2H, NCH_2), 9.34 (br. s, 1H, OH). ^{13}C NMR (CD_3OD) δ: 23.23 (br. t, $2CH_2$, ^1J 127.4 Hz), 25.86 (br. t, CH_2, ^1J 125.8 Hz), 33.82 (br. t, $2CH_2$, ^1J 125.2 Hz), 45.98 (t, NCH_2, ^1J 142.9 Hz), 80.68 (m, NCN), 171.54 (t, C=O, ^2J 4.3 Hz). IR (KBr, ν/cm^{-1}): 3228 (NH), 3056, 2957, 2925, 2872, 2855 (CH_2), 2770 (br), 2614 (br, OH), 1716 (C=O), 1696 (sh), 1503, 1446, 1429, 1373, 1352, 1336, 1305, 1280, 1256, 1245, 1173, 1149, 1081, 1060, 1046, 1021, 961, 945, 933, 912, 885, 840, 683, 581, 541, 513, 461.

6c: yield 54%, mp 139–140 °C (dioxane). ^1H NMR (CD_3OD) δ: 0.92 (t, 3H, CH_2Me, ^3J 7.4 Hz), 1.35 (s, 3H, N_2CMe), 1.67 (dq, 1H, CH_AH_BMe, ^2J 14.4 Hz, ^3J 7.2 Hz), 1.72 (dq, 1H, CH_AH_BMe, ^2J 14.4 Hz, ^3J 7.2 Hz), 3.36 (d, 1H, NCH_AH_B, ^2J 16.2 Hz), 3.41 (d, 1H, NCH_AH_B, ^2J 16.2 Hz). ^1H NMR ([$^2H_6$]DMSO) δ: 0.79 (t, 3H, CH_2Me, ^3J 7.3 Hz), 1.18 (s, 3H, N_2CMe), 1.49 (dq, 1H, CH_AH_BMe, ^2J 12.5 Hz, ^3J 7.2 Hz), 1.52 (dq, 1H, CH_AH_BMe, ^2J 12.5 Hz, ^3J 7.3 Hz), 2.98 (br. s, 1H, NH), 3.13 (br. d, 1H, NCH_AH_B, ^2J 16.1 Hz), 3.19 (br. d, 1H, NCH_AH_B, ^2J 16.1 Hz), 9.43 (br. s, 1H, OH). ^{13}C NMR (CD_3OD) δ: 7.96 (qt, CH_2Me, ^1J 126.0 Hz, ^2J 4.0 Hz), 23.25 (q, N_2CMe, ^1J 127.0 Hz), 31.67 (tq, CH_2Me, ^1J 126.6 Hz, ^2J 3.7 Hz), 46.46 (t, NCH_2, ^1J 143.2 Hz), 81.15 (m, NCN), 171.29 (t, C=O, ^2J 4.7 Hz). IR (KBr, ν/cm^{-1}): 3231 (NH), 2977, 2944, 2884 (Me, CH_2), 2683 (br), 2536 (br, OH), 1715 (sh), 1704 (C=O), 1698 (sh), 1518, 1469, 1441, 1384, 1374 (sh), 1343, 1312, 1284, 1245, 1230 (sh), 1160, 1112, 1073, 1052, 1029, 960, 903, 849, 695, 592, 533.

7 (MeOH, δ 171.1 ppm; [$^2H_6$]DMSO, δ 170.1 ppm)[9(b)] and its methoxynitrone derivative **8** (MeO–C=N→O) (MeOH, δ 156.7 ppm; [$^2H_6$]DMSO, δ 150.5 ppm).[9(b)]

It is well known[7,8] that unsubstituted HAs RC(O)NHOH, bearing electron-withdrawing substituents in R group, dissociate to form solely the ambident anion A [(A_1) O=C–N$^-$–OH ⟷ ($^-$O–C=N–OH) (A_2)], and thus belong to NH acids. In fact, the molecule of GlyHA in a crystalline state exists as the zwitterion $NH_3^+CH_2C(O)N^-OH$ (B), containing a deprotonated amide N atom and a planar hydroxamate-anionic group of *cis* configuration.[10] Moreover, the comparison of the bond lengths of the GlyHA amide group [C=O, 1.296(2) Å and C_{sp^2}–N, 1.294(3) Å][10] with the mean X-ray diffraction lengths of the corresponding bonds for secondary acyclic amides [C=O, 1.231 Å and C_{sp^2}–N, 1.334 Å][11(a)] indicates a high contribution of the A_2 resonance structure in crystalline GlyHA.

Based on a comparison of the dissociation macroconstants of protonated (pK_1 7.50 in 0.1 M $NaClO_4$) and unprotonated (pK_2 9.26)[12] forms of GlyHA, it was concluded[1(b)] that the NH_3^+ group is more acidic than the NHOH group. Bearing in mind that GlyHA was employed in the reactions with ketones as a suspension in methanol,† namely, as a zwitterion (*vide supra*), it can be suggested that the protonation of ketone may be ascribed to the NH_3^+ group of B dipolar form of GlyHA rather than to the NHOH group of its possible[1(b)] equilibrium neutral form in solution. The subsequent reaction of the protonated ketone with the liberated amine group of GlyHA results in the formation of the intermediate oxonic anion $Me_2C(OH_2^+)NHCH_2C(O)N^-OH$[13] and the $Me_2C^+NHCH_2C(O)$–N^-OH[13] carbocation (protonated azomethine), which undergoes regioselective cyclization.

This reaction mechanism (Scheme 1) is probably coinciding with one of acid-catalysed condensation of α-amino amides with carbonyl compounds,[14] which leads to imidazolidin-4-ones. However, in our case, the reaction is self-catalysed, that may be attributed to the significantly higher acidity of HAs relative to the amides.[7,8]

The following features of the molecular structure of spiro HA **6a** in crystal (Figure 1)‡ should be mentioned.

(i) The hydroxamic fragment O=C–N–O is non-planar (φ_{exo} 17.9°), as confirmed by the displacement of the O(1) atom (0.374 Å) from the N(3)C(4)C(5)O(2) mean plane (to within ±0.0005 Å). Moreover, the synperiplanar (*sp*) twist of the hydroxamic fragment causes the spiral chirality of *P*- (plus, $\varphi_{exo} > 0$) (Figure 1) or *M*-type (minus, $\varphi_{exo} < 0$)[15] depending on the heterocycle conformation chirality of N- ($\tau_2 > 0$) or S-type ($\tau_2 < 0$), respectively.

(ii) The amide N(3) atom is non-planar [$\Sigma\omega$ N(3) = 350.9°, the height of a shallow pyramid is equal to 0.247 Å] because of an opposite character of skew of exo- (φ_{exo}) and endocyclic ($\tau_0 = -15.6°$) dihedral angles at the N(3)–C(4) bond and by the influence of an attached electronegative O(1) α-substituent.[16] The decrease of the amide n_N–π*(C=O) resonance displays also in weakened N(3)–C(4) and strengthened C(4)=O(2) bonds in **6a** (Figure 1) as compared with the averaged lenghts [N–C(O) 1.335(1) Å, C=O 1.232(1) Å][11(b)] of the corresponding bonds of γ-lactams in crystals.

(iii) The lone electron pair (LP) at the pyramidal sp^3-configuration amine N(1) atom [$\Sigma\omega$ N(1) = 315°] is pseudo-*e* oriented, assisting to the $n_{N(1)}$–$\sigma^*_{C(2)-N(3)}$ anomeric effect[16] [φ $LP_{N(1)}$N(1)C(2)N(3) –157°]. This effect leads to the lengthening of the C(2)–N(3) bond in the molecule of **6a** (Figure 1) as compared to the mean X-ray diffraction length [1.455(1) Å][11(b)] of the N–$C_β$ bond in γ-lactams. Moreover, there is the mutual antiperiplanar (*ap*) orientation: (*a*) of $LP_{N(1)}$ and $LP_{N(3)}$ {pseudo-dihedral angle φ [$LP_{N(1)}$N(1)N(3)$LP_{N(3)}$] is equal to 150°}, that

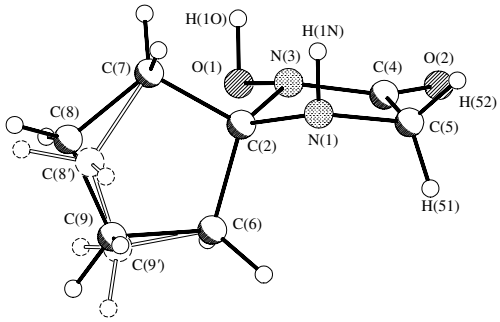


Figure 1 Molecular structure of hydroxamic acid **6a** [is illustrated as (*P*,1*R*,3*S*)-enantiomer]. Selected bond lengths (Å): O(1)–N(3) 1.391(1), N(1)–C(2) 1.475(2), N(1)–C(5) 1.474(2), O(2)–C(4) 1.218(2), C(2)–N(3) 1.474(2), C(2)–C(6) 1.545(2), C(2)–C(7) 1.530(2), N(3)–C(4) 1.342(2), C(4)–C(5) 1.513(2); selected bond and dihedral angles (°): C(2)–N(1)–C(5) 105.8(1), N(1)–C(2)–N(3) 100.1(1), N(1)–C(2)–C(6) 113.1(1), N(1)–C(2)–C(7) 112.5(1), N(3)–C(2)–C(6) 112.0(1), N(3)–C(2)–C(7) 114.0(1), C(6)–C(2)–C(7) 105.4(1), O(1)–N(3)–C(2) 118.1(1), O(1)–N(3)–C(4) 120.0(1), C(2)–N(3)–C(4) 112.8(1), O(2)–C(4)–N(3) 126.9(1), O(2)–C(4)–C(5) 127.6(2), N(3)–C(4)–C(5) 105.5(1), N(1)–C(5)–C(4) 105.0(1); H(1O)–O(1)–N(3)–C(2) 123.5, H(1N)–N(1)–C(2)–N(3) 77.7, C(5)–N(1)–C(2)–N(3) (τ_3) –31.7(1), C(5)–N(1)–C(2)–C(7) –153.1(1), H(1N)–N(1)–C(5)–H(51) 156.8, H(1N)–N(1)–C(5)–H(52) 33.0, C(2)–N(1)–C(5)–C(4) (τ_2) 24.3(2), N(1)–C(2)–N(3)–C(4) (τ_4) 30.2(1), C(6)–C(2)–N(3)–O(1) 57.1(1), C(7)–C(2)–N(3)–O(1) –62.5(2), C(7)–C(2)–N(3)–C(4) 150.5(1), O(1)–N(3)–C(4)–O(2) (φ_{exo}) 17.9(2), O(1)–N(3)–C(4)–C(5) –161.9(1), C(2)–N(3)–C(4)–O(2) 164.2(2), C(2)–N(3)–C(4)–C(5) (τ_0) –15.6(2), N(3)–C(4)–C(5)–N(1) (τ_1) –5.7(2), C(7)–C(2)–C(6)–C(9) (τ'_1) –17.3(2), C(7)–C(2)–C(6)–C(9′) (τ''_1) –0.8(3), C(6)–C(2)–C(7)–C(8) (τ'_0) –10.2(2), C(6)–C(2)–C(7)–C(8′) (τ''_0) 21.9(4), C(2)–C(6)–C(9)–C(8) (τ'_2) 37.9(2), C(2)–C(6)–C(9′)–C(8′) (τ''_2) –21.3(6), C(2)–C(7)–C(8)–C(9) (τ'_4) 34.6(2), C(2)–C(7)–C(8′)–C(9′) (τ''_4) –35.2(6), C(7)–C(8)–C(9)–C(6) (τ'_3) –44.5(2), C(7)–C(8′)–C(9′)–C(6) (τ''_3) 35.7(7).

6d: yield 27%, mp 164–165 °C (THF). ^{1}H NMR (CD_3OD) δ: 1.04 (s, 9H, Bu^t), 1.37 (s, 3H, Me), 3.38 (s, 2H, CH_2, $\Delta\nu_{AB} \to 0$). ^{1}H NMR (C_6D_6) δ: 0.98 (s, 9H, Bu^t), 1.15 (s, 3H, Me), 2.98 (d, 1H, CH_AH_B, ^2J 15.8 Hz), 3.10 (d, 1H, CH_AH_B, ^2J 15.8 Hz), 3.55 (br. s, 1H, NH), 10.9 (br. s, 1H, OH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 19.54 (q, N_2CMe, ^1J 126.1 Hz), 25.93 (qm, CMe_3, ^1J 124.6 Hz, ^3J 4.4 Hz), 39.22 (m, CMe_3), 46.06 (t, CH_2, ^1J 141.9 Hz), 82.77 (m, NCN), 169.07 (t, C=O, ^2J 4.5 Hz). IR (KBr, ν/cm^{-1}): 3321 (NH), 3013, 3000, 2983, 2963, 2933, 2873 (Me, CH_2), 2740 (br), 2716 (br), 2605 (br, OH), 1717 (C=O), 1689 (sh), 1536, 1508, 1469, 1457, 1442, 1417, 1394, 1377, 1301, 1225, 1202, 1185, 1131, 1086, 1058, 1043, 1021, 987, 925, 908, 865, 800, 687, 593, 568, 548, 528, 452, 421.

6e: yield 53%, mp 151–152 °C (MeCN). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.61 (s, 3H, Me), 3.10 (dd, 1H, NCH_AH_B, ^2J 16.0 Hz, $^3J_{NH}$ 9.0 Hz), 3.27 (dd, 1H, NCH_AH_B, ^2J 16.0 Hz, $^3J_{NH}$ 8.2 Hz), 3.49 (dd, 1H, NH, ^3J 9.0 Hz, ^3J 8.2 Hz), 7.29 (m, 1H, Ph), 7.33 (m, 2H, Ph), 7.47 (m, 2H, Ph), 9.71 (br. s, 1H, OH). ^{1}H NMR ([$^2H_6$]acetone) δ: 1.73 (s, 3H, Me), 3.26 (d, 1H, NCH_AH_B, ^2J 16.1 Hz), 3.36 (d, 1H, NCH_AH_B, ^2J 16.1 Hz), 7.31 (m, 1H, Ph), 7.36 (m, 2H, Ph), 7.60 (m, 2H, Ph). ^{13}C NMR ([$^2H_6$]DMSO) δ: 24.44 (q, Me, ^1J 127.8 Hz), 45.30 (t, CH_2, ^1J 142.0 Hz), 79.78 (m, NCN), 126.04 (dm, $2C_{Ph}$, ^1J 159.0 Hz), 127.78 (dm, p-C_{Ph}, ^1J 160.5 Hz), 128.23 (dm, $2C_{Ph}$, ^1J 160.8 Hz), 142.53 (m, i-C_{Ph}), 170.18 (t, C=O, ^2J 4.1 Hz). IR (KBr, ν/cm^{-1}): 3246 (NH), 3060, 2931, 2855 (Me, CH_2), 2575 (br), 2534 (br, OH), 1717 (sh), 1704 (C=O), 1618, 1584, 1553, 1542, 1533, 1510, 1445, 1380, 1363, 1318, 1307, 1273, 1213, 1193, 1159, 1117, 1092, 1077, 1041, 992, 956, 885, 871, 854, 766, 704, 675, 642, 593, 565, 492, 426.

‡ *Crystallographic data for* **6a**: at 298 K the crystals of $C_7H_{12}N_2O_2$ are monoclinic, space group $P2_1/n$, a = 9.938(2), b = 8.944(2) and c = 10.124(2) Å, β = 117.13(1)°, V = 800.9(3) Å^3, Z = 4, M = 156.19, d_{calc} = 1.295 g cm^{-3}, μ(MoKα) = 0.96 cm^{-1}, F(000) = 336. The intensities of 2257 reflections were measured on a Siemens P3/PC diffractometer at 298 K [λ(MoKα) = 0.71072 Å, $\theta/2\theta$-scans, $2\theta < 58°$], and 2143 independent reflections (R_{int} = 0.0280) 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. The analysis of the Fourier electron density synthesis revealed that the C(8) and C(9) atoms are disordered by two positions with the occupancies 0.77 [C(8), C(9)] and 0.23 [C(8′), C(9′)]. Hydrogen atoms for the ordered part of the molecule were located from the Fourier synthesis and refined in the isotropic approximation. The refinement converged to wR_2 = 0.1457 and GOF = 1.038 for all independent reflections [R_1 = 0.0468 was calculated against F for 1498 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). 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 1135/16.

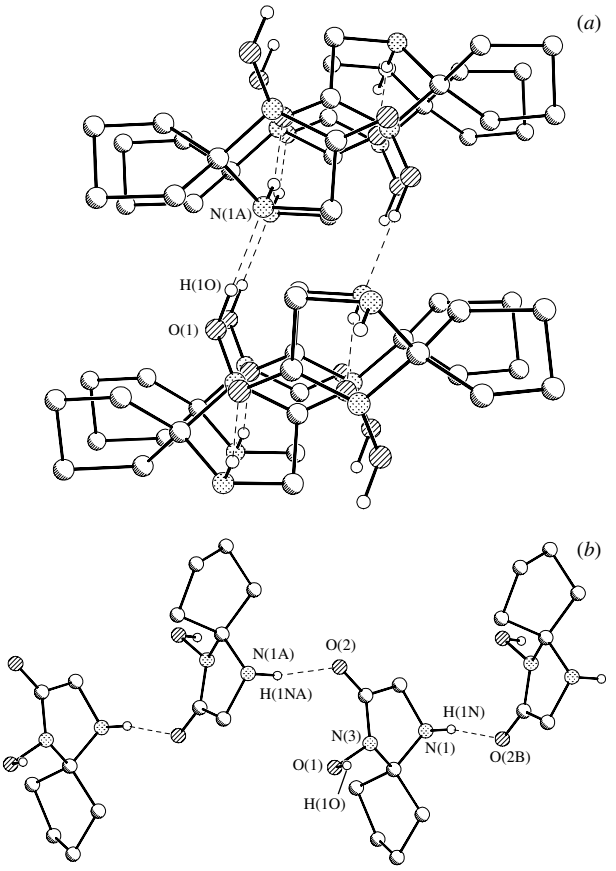
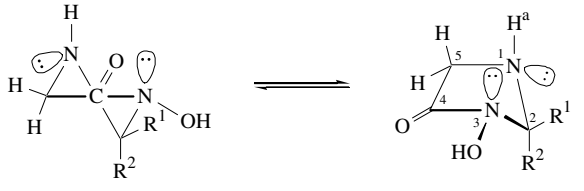


Figure 2 (*a*) Fragment of a heterochiral layer consisting of alternate chiral columns of opposite handedness in the crystal structure of **6a** (perspective view on the *bc* plane). Hydrogen bonds are shown by dashed lines. The geometric parameters of H-bonds are as follows: H(1O)···N(1) 1.773 Å, O(1)···N(1) 2.693 Å, O(1)–H(1O)···N(1) 167.6°; H(1N)···O(2) 2.092 Å, N(1)···O(2) 2.978 Å, N(1)–H(1N)···O(2) 167.0°. [The symmetry transformation used to generate the atoms N(1) ($x + 1/2$, $-y + 3/2$, $z + 1/2$) and O(2) ($-x + 3/2$, $y + 1/2$, $-z + 1/2$)]. (*b*) Hydrogen-bonded infinite homochiral chain [(*P*,1*R*,3*S*)-enantiomers] along the crystallographic *b* axis in the crystal structure of **6a**.

corresponds to a preferable *trans* orientation of LPs of the geminal N atoms in cyclic aminals;[17] and (*b*) as of N(1)–C(2) and N(3)–O(1) [φ N(1)C(2)N(3)O(1) 177.2°], and also of N(1)–C(5) and C(4)=O(2) polar bonds [φ N(1)C(5)C(4)O(2) 174.5°], which additionally stabilises the heterocycle conformation of HA **6a** in a crystal.

(iv) According to the calculated phase angle (*P*) and amplitude of puckering (τ_m),[4,18] the chiral N-type (*vide supra*) heterocycle conformation of (*P*, 1*R*, 3*S*)-**6a** enantiomer in a crystal (Figure 1) is intermediate (P_N 43.8°, τ_m 33.7°) between the forms of a pure half-chair ${}^{N(1)}_{C(2)}T$ (P_N 36°) and an envelope ${}_{C(2)}E$ (P_N 54°) (Scheme 2). The corresponding phase angle P_S for the S-type heterocycle form of (*M*, 1*S*, 3*R*)-**6a** enantiomer is equal to 223.8°.

(v) The spiro cyclopentane ring in the molecule of **6a** in a crystal is disordered and adopts two opposite chirality conformations (*cf.* the signs of torsional angles τ' and τ'', Figure 1). The dominant (77%) conformation **A** is the folded half-chair



${}^{N(1)}_{C(2)}T$, P_N 36° (*P*, 1*R*, 3*S*)-**6a** ${}_{C(2)}E$, P_N 54°

Scheme 2

[P_N 31.5°, τ_m 44.5°, $\tau'_2 > 0$ for (*P*, 1*R*, 3*S*)-**6a**, and P_S 211.5°, $\tau'_2 < 0$ for (*M*, 1*S*, 3*R*)-**6a**]. The less populated (23%) conformation **B** of a cyclopentane ring in (*P*, 1*R*, 3*S*)-**6a** (Figure 1) is close to the ${}^{C(8')}E$ envelope ($\tau''_1 = -0.8°$) but substantially more flattened (P_S 235°, τ_m 37.1°, $\tau''_2 < 0$) as compared with the ideal envelope (Cs) for cyclopentane ($\tau_1 = 0$, $|\tau_0| = |\tau_2| = 28.6°$, $|\tau_3| = |\tau_4| = 46.1°$, P_N 54° or P_S 234°, τ_m 48.7°).[19] As expected, in both of these conformations (**A** and **B**), the spiro cyclopentane ring is almost orthogonal to the heterocycle {φ [(C(5)N(1)C(2)C(6)] 87.7°; φ [C(4)N(3)C(2)C(6)] –89.9°}.

In summary, the increase of the bulkiness of substituents implanted on the C(2) atom of the heterocycle of **6a** has almost no effect on the heterocycle form in a crystal as compared with such a form for **1** {*cf.* φ_{exo} 19.3°, τ_0 –14.9°, P_N 44.4°, τ_m 31.4°, $\Sigma\omega$ N(1) 317.2°, $\Sigma\omega$ N(3) 350.8°, φ [$LP_{N(1)}$N(1)C(2)N(3)] –152.5°, φ [$LP_{N(1)}$N(1)N(3)$LP_{N(3)}$] 154°}[4] but significantly changes the crystal structure of **6a**, which is formed by the same types of intermolecular H-bonds as in **1**. Thus, achiral HA **1** crystallises from acetone as a racemic mixture of chiral crystals (mp 177–178 °C, space group $P2_12_12_1$, $Z = 4$)[4] consisting of (*P*, 1*R*, 3*S*) and (*M*, 1*S*, 3*R*) enantiomers, whereas achiral spiro HA **6a** crystallises from ethanol to give racemic crystals (mp 153–154 °C, space group $P2_1/n$, $Z = 4$) of the same type enantiomers. The racemic crystals of **6a** consist of heterochiral layers, which are turned to each other by hydrophobic bulky cyclopentane rings [Figure 2(*a*)]. These layers are formed by the strong O–H···N type H-bond along the crystallographic trend [101], which connects the alternately situated columns of opposite chirality [Figure 2(*a*)], and by a weak[20] intermolecular H-bond of the N–H···O=C type, which forms infinite homochiral chains [Figure 2(*b*)] along the crystallographic *b* axis. The intramolecular H-bond of the O–H···O=C type is not formed in the crystals of **6a** {$d_{H(1O)\cdots O(2)}$ 2.98 Å, φ [H(1O)O(1)N(3)C(4)] –91.9°} and **1**.[4]

Thus, we found that the condensation of GlyHA with aliphatic ketones and acetophenone results in the formation of five-membered cyclic HAs, whereas the condensation of GlyHA and other α-amino HAs with aldehydes affords six-membered hydroxamates or acyclic azomethins.[6] Taking into consideration published data[5] on AlaHA, it can be assumed that the regioselective N-aminoalkylation is a common trend of the reactions of non-aromatic α-amino hydroxamic acids with ketones.

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