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1-[(1-Ethoxypropylidene)amino]-2-ethyl-4-(4-hydroxybenzyl)imidazol-5(4*H*)-one

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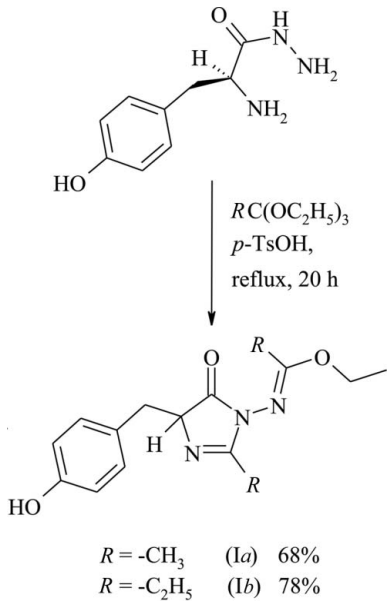
The racemic title compound, $C_{17}H_{23}N_3O_3$, isolated from the reaction of L-(−)-tyrosine hydrazide with triethyl orthopropionate in the presence of a catalytic quantity of *p*-toluenesulfonic acid (*p*-TsOH), crystallizes with $Z' = 1$ in a centrosymmetric monoclinic unit cell. The molecule contains two planar fragments, *viz.* the benzene and imidazole rings, linked by two C—C single bonds. The dihedral angle between the two planes is 59.54 (5)° and the molecule adopts a synclinal conformation. The HOMA (harmonic oscillator model of aromaticity) index, calculated for the benzene ring, demonstrates no substantial interaction between the two π-electron delocalization regions in the molecule. In the crystal structure, there is an O—H···N hydrogen bond that links the molecules along the *c* axis.

Comment

Carboxylic acid hydrazides constitute useful precursors for the synthesis of nitrogen- and nitrogen/oxygen-containing heterocycles. Numerous transformations of this class of compounds are known to lead to four-membered azetidines (Amr *et al.*, 2008), five-membered pyrroles (Alawandi & Kulkarni, 2006), 1,3,4-oxadiazoles (Dabiri *et al.*, 2006; Leiby, 1984) or 1,2,4-triazoles (Francis *et al.*, 1991; Taha & El-Badry, 2007) and to six-membered systems such as substituted pyrimidines (Elgemeie *et al.*, 2001), oxadiazines (Dubey *et al.*, 2005) or triazines (Neunhoeffer & Klein-Cullmann, 1992; Lobanov *et al.*, 1991). One subgroup of the hydrazide family is the class of α-aminocarboxylic acid hydrazides, which are compounds containing at least two potential reaction sites. They react with equimolar quantities of triethyl orthoesters to yield 2-(1-amino-1-phenylmethyl)-1,3,4-oxadiazoles and 1,2,4-triazin-6-ones (Kudelko *et al.*, 2011). We found that the product formed depends strongly on the basicity of the amino group, which is influenced by the electronic nature and steric hindrance of substituents adjacent to the α-C atom. In contrast, transformations conducted with excess orthoester may follow a different path due to the fact that both nitrogen nucleophilic centres may react fully with the ethoxymethylene synthon. Thus, heating of L-(−)-tyrosine hydrazide in an excess of the orthoester resulted in the formation of another five-membered heterocycle, namely 1-[(1-ethoxypropylidene)amino]-4-(4-hydroxybenzyl)imidazol-5(4*H*)-one, (I). Imidazole derivatives have attracted interest in medicinal chemistry mainly for their antifungal, antiprotozoal and antihypertensive activities (Mutnick, 2010). They have also been utilized as corrosion inhibitors, as ionic liquids, and for the production of thermally stable polymers (Grimmet, 1984; Lin, 1988). We report here the synthesis and crystal structure of the title compound, (I*b*), which resulted from the reaction of L-(−)-tyrosine hydrazide with triethyl orthopropionate in the presence of a catalytic quantity of *p*-toluenesulfonic acid (*p*-TsOH).



R = -CH_3 (I*a*) 68%
R = -C_2H_5 (I*b*) 78%

Compound (I*b*) is racemic and crystallizes in a centrosymmetric monoclinic space group with one molecule (isomer) in the asymmetric unit. The molecular structure of (I*b*) (isomer 4*R*) is depicted in Fig. 1, and selected geometric data are given in Table 1. In the studied molecule, two planar fragments may be distinguished, *viz.* the benzene and imidazole rings, linked by two C—C single bonds. These rings are not coplanar, the dihedral angle between them being 59.54 (5)°. An intramolecular C9—H9*B*···N1 hydrogen bond (Table 2) forms a five-membered quasi-ring which makes a dihedral angle of 73.82 (6)° with the imidazole ring. The molecule of (I*b*) adopts a synclinal conformation with respect to rotation around the C4—C16 bond. A density functional theory (DFT) study also predicts this conformation as the preferential one for an isolated molecule of (I*b*). The remaining rotamers resulting from the former rotation of 60° along the C4—C16 bond are less stable in the following order: synclinal by 0.40–0.82 kcal mol^{-1}, antiperiplanar by 2.12–2.23 kcal mol^{-1}, anticlinal by 2.51–3.24 kcal mol^{-1}, synperiplanar by 5.42–

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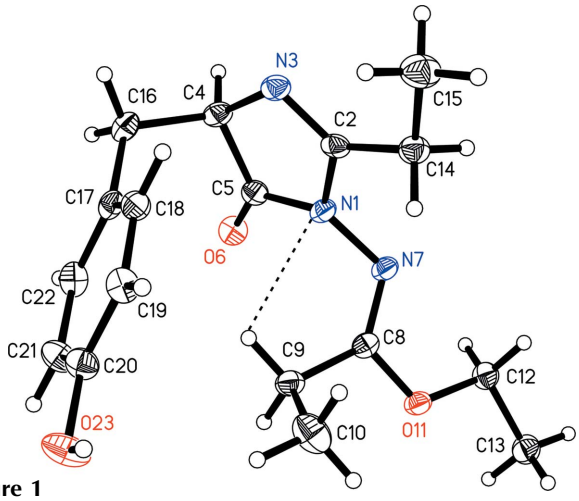

Figure 1
The molecular structure of (I*b*) (isomer 4*R*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. The dashed line indicates the intramolecular hydrogen bond.

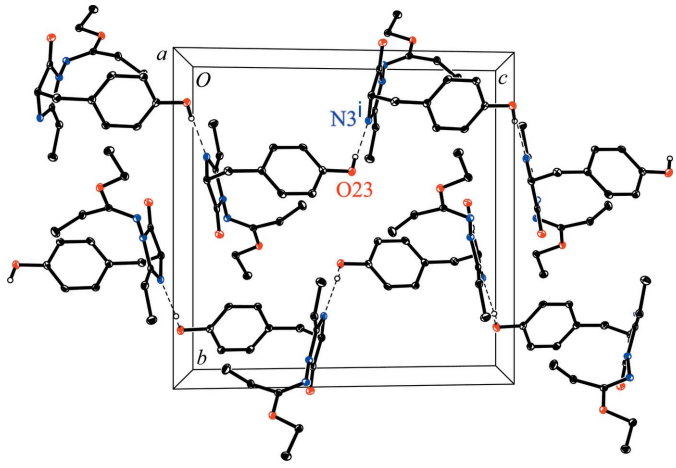

Figure 2
A packing diagram for (I*b*), showing the O23—H23···N3^{i} hydrogen bonds as dashed lines. [Symmetry code: (i) $x, -y+\frac{1}{2}, z+\frac{1}{2}$.]

5.97 kcal mol^{-1} and anticlinal by 6.14–6.42 kcal mol^{-1} (1 kcal mol^{-1} = 4.184 kJ mol^{-1}). Amide atom N1 lies only 0.118 (1) Å out of the plane defined by the three neighbouring atoms (C2, C5 and N7). Therefore, the sum of the valence angles around atom N1 of 357.85 (9)° demonstrates sp^2 hybridization (360° for sp^2 and 328° for sp^3). The N1—N7 bond length is typical of the N—N distance between two trigonal N atoms (Allen *et al.*, 1987). The imidazolone group contains two localized double bonds [O6═C5 = 1.2158 (13) Å and N3—C2 = 1.2788 (13) Å], the lengths of which are in good agreement with the literature data (Nalepa *et al.*, 1999; Zhang & Jiao, 2006; Sun *et al.*, 2007) and similar ring systems found in the Cambridge Structural Database (CSD, *ConQuest* Version 1.13; Allen, 2002). Two C—N bonds located between them (N1—C2 and N1—C5) exhibit intermediate values due to π-electron delocalization between the C═N and C═O groups. The other two bonds within the imidazole ring (N3—C4 and C4—C5) are common single bonds. In the studied molecule, the remaining bond lengths and angles are not unusual. There are no significant differences between the geometry of (I*b*) in the crystalline state and the calculated structure; the differences do not exceed 0.02 Å for bond lengths, 2° for bond angles and 10° for torsion angles.

To estimate the influence of π-electron delocalization in the imidazolone group on the aromaticity of the benzene ring, the HOMA (harmonic oscillator model of aromaticity) index (Kruszewski & Krygowski, 1973; Krygowski, 1993) was calculated. This descriptor of aromaticity is a leading method for the quantitative determination of cyclic π-electron delocalization in chemical compounds. It is based on the geometric criterion of aromaticity, which stipulates that bond lengths in aromatic systems are between values that are typical for single and double bonds (Kruszewski & Krygowski, 1973; Krygowski, 1993). Therefore, HOMA = 0 for a model non-aromatic system, *e.g.* the Kekulé structure of benzene, and HOMA = 1 for the system with all bonds equal to the optimal value, assumed to be realised for fully aromatic systems. The HOMA value [based on B3LYP/6-311++G(d,p) optimized geometries] for the benzene ring of (I*b*) (0.983) is almost identical to the value calculated for the 4-methylphenol ring (0.984). This result is evidence that the regions of π-electron delocalization in the molecule of (I*b*) are separated from each other and do not interact significantly.

The crystal structure of (I*b*) is presented in Fig. 2. The –OH substituent on the benzene ring forms an intermolecular hydrogen bond with atom N3 of the imidazole ring of a neighbouring molecule. These interactions form zigzag chains extending along the *c* axis.

Experimental

L-(−)-Tyrosine hydrazide (1.95 g, 10 mmol) was added to a mixture of triethyl orthopropionate (8.88 g, 50 mmol, 10 ml) and *p*-TsOH (0.1 g) and kept under reflux for 20 h (thin-layer chromatography). After cooling, the mixture was washed with water (30 ml), dried over $MgSO_4$ and then concentrated under reduced pressure. The crude solid was crystallized from ethyl acetate to give colourless crystals of (I*b*) (yield: 2.47 g, 78%; m.p. 446–448 K). $[\alpha]_D^{20}$ 0.0 (MeOH, *c* 1). Analysis calculated for $C_{17}H_{23}N_3O_3$: C 64.32, H 7.32, N 13.23%; found: C 64.19, H 7.27, N 13.29%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.78 (3H, *t*, *J* = 7.5 Hz, C2—*R*: CH_2CH_3), 1.02 (3H, *t*, *J* = 7.5 Hz, N1—*R*: CH_2CH_3), 1.22 (3H, *t*, *J* = 7.2 Hz, OCH_2CH_3), 1.47–1.67 (2H, *m*, *R*: CH_2CH_3), 2.21 (2H, *q*, *J* = 7.5 Hz, *R*: CH_2CH_3), 2.80–2.87 (1H, *dd*, *J* = 6.0 and 13.8 Hz, Ph—CH_2–), 3.02–3.09 (1H, *dd*, *J* = 6.0 and 13.8 Hz, Ph—CH_2–), 4.18 (2H, *q*, *J* = 7.2 Hz, OCH_2CH_3), 4.29 (1H, *br s*, C4: H), 6.59 (2H, *d*, *J* = 7.8 Hz, Ar: H3′, H5′), 6.92 (2H, *d*, *J* = 7.8 Hz, Ar: H2′, H6′), 9.17 (1H, *s*, OH). ^{13}C NMR (DMSO-d_6): δ 9.2, 9.4, 13.8, 21.3, 22.0, 35.0, 63.1, 66.5, 114.4, 126.1, 130.5, 156.1, 164.0, 175.5, 176.2.

Crystal data

$C_{17}H_{23}N_3O_3$
M_r = 317.38
Monoclinic, $P2_1/c$
a = 7.9622 (2) Å
b = 14.3492 (4) Å
c = 14.6469 (4) Å
β = 97.210 (2)°
V = 1660.19 (8) Å^3
Z = 4
Mo *Kα* radiation
μ = 0.09 mm^{-1}
T = 100 K
0.22 × 0.18 × 0.15 mm

Table 1
Selected geometric parameters (Å, °).

N1—C5	1.3746 (14)	N3—C4	1.4692 (14)
N1—C2	1.3984 (14)	C4—C5	1.5147 (15)
N1—N7	1.4127 (12)	C4—C16	1.5358 (15)
C2—N3	1.2788 (13)	N7—C8	1.2878 (14)
C2—C14	1.4860 (16)	C16—C17	1.5082 (15)
C5—N1—C2	109.64 (9)	N1—C2—C14	119.42 (9)
C5—N1—N7	124.73 (9)	C2—N3—C4	107.27 (9)
C2—N1—N7	123.47 (9)	N3—C4—C5	105.50 (9)
N3—C2—N1	113.54 (10)	N3—C4—C16	111.69 (9)
N3—C2—C14	127.00 (10)	C5—C4—C16	112.41 (9)
N3—C4—C16—C17	−67.46 (12)	C5—C4—C16—C17	50.90 (13)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O23—H23···N3^{i}	0.881 (16)	1.857 (16)	2.7279 (13)	169.5 (14)
C9—H9*B*···N1	0.97	2.41	2.8086 (14)	104

Symmetry code: (i) $x, -y+\frac{1}{2}, z+\frac{1}{2}$.

Data collection

Oxford Xcalibur CCD area-detector diffractometer
12349 measured reflections
3799 independent reflections
2771 reflections with $I > 2\sigma(I)$
$R_{int} = 0.034$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.085$
$S = 0.92$
3799 reflections
211 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.25$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}

The molecular geometries of the (I*b*) isomers were optimized using standard density functional theory (DFT) and employed the B3LYP hybrid function (Becke, 1988, 1993; Lee *et al.*, 1988) with the 6-311++G** level of theory. All species corresponded to the minima at the B3LYP/6-311++G** level with no imaginary frequencies. The conformational energy was calculated at the 6-311++G** level. In each rotamer, the geometric parameters were fully relaxed, except for the constrained C17—C16—C4—N3 torsion angle. The values of this angle were chosen using a step size of 10° within the range −180 to 180°. All calculations were performed using the *GAUSSIAN09* program package (Frisch *et al.*, 2010).

All H atoms were generated in idealized positions and treated as riding, with C—H = 0.93 (aromatic), 0.96 (methyl), 0.97 (methylene) or 0.98 Å (methine) and with U_{iso}(H) = 1.5U_{eq}(C,O) for methyl and hydroxy groups and 1.2U_{eq}(C) otherwise. The position of the O-bound H atom was refined.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2008); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2008); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3431). Services for accessing these data are described at the back of the journal.

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