On the isomerism/tautomerism of hydrazones. Crystal structures, study in solution and theoretical calculations of new series of α-N-heterocyclic hydrazones

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The isomerism/tautomerism of new series of α-N-heterocyclic hydrazones with chelating properties towards metal ions and potential biological activity have been studied in the solid state by X-ray crystallography and in solution by nuclear magnetic resonance. Among possible *syn-Z*/*anti-E* isomers and different tautomeric structures, the molecular structures of dimethylquinolylhydrazone **5** and its phthalazinyl analogue **6** have shown that both are *anti-E* isomers. In **5** the mobile proton resides on the hydrazone nitrogen, but in the phthalazine derivative **6** it is located on one endocyclic nitrogen. The same isomeric structures are also confirmed in the solution by NMR experiments. While for **6** no other isomer is detected, the quinoline derivatives **1**–**5** show chemical equilibrium between the imino and amino tautomers in the solution, the latter being present in a very high amount (>90%). The study has also been extended to potential energy calculations of isolated molecules and of molecules in the crystal lattice.

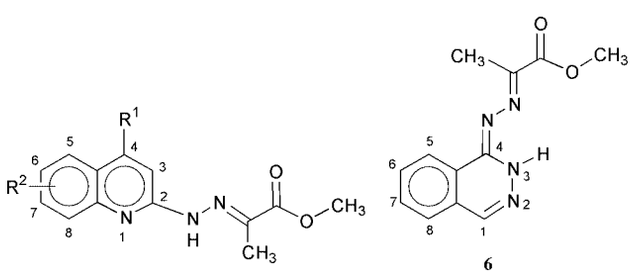
N-Acyl- and *N*-arylhydrazones constitute important classes of organic compounds. Among them, N-heterocyclic hydrazone derivatives have received a lot of interest in view of their coordination properties. They may act as mono- or polydentate ligands towards metal ions,[1,2] and several metal complexes have been synthesized and characterized.[3] Furthermore, these compounds may exhibit pharmacological activities. As an example, phthalazin-1(2*H*)-one causes site-specific DNA damage[4] and mutagenic effects.[5]

An interesting aspect of the chemistry of heterocycles is represented by the existence of prototropic tautomerism.[6] As tautomeric structures have different aromaticity and reactivity,[7] their structural characterization plays an important role in heterocyclic chemistry.

Acidic hydrogen atoms of hydrazino- and dihydrazinophthalazine derivatives are quite mobile, allowing tautomeric equilibria involving the endocyclic and exocyclic nitrogen atoms (annular and side-chain tautomerism).[6] These equilibria can be affected by complexation with metal ions.[8] Recently it has been shown that hydrazones derived from thiophenecarbaldehydes and 2-hydrazinoquinoline can exist as *syn-Z* or *anti-E* isomers with different tautomeric forms.[9]

In the ambit of a general project devoted to the structural characterization of heterocyclic compounds,[10–12] aimed at obtaining information on isomerism/tautomerism of heterocyclic hydrazones, we wish to report here on the structural characterization and tautomeric properties of new series of α-*N*-quinolyl- and -phthalazinylhydrazones (**1**–**6**). Their *anti-E* isomers are depicted in Scheme 1.[13,14]

Different *syn-Z*/*anti-E* configurations of the hydrazone double bond and tautomeric structures, depending on the location, *i.e.* endocyclic or exocyclic, of the mobile proton might be produced. As an example, the possible isomers of the quinolylhydrazones **1**–**5** are reported in Scheme 2.



1 R^1, R^2 = H
2 R^1 = CH_3, R^2 = H
3 R^1 = CH_3, R^2 = 6-CH_3
4 R^1 = CH_3, R^2 = 7-CH_3
5 R^1 = CH_3, R^2 = 8-CH_3

6

Scheme 1

As the aliphatic side chain is the same for all compounds, it is interesting to evaluate the role played by different heterocyclic nuclei in the isomerism and tautomerism of compounds **1**–**6**. The study has been carried out in the crystal state by X-ray crystallography, and in solution by using different nuclear magnetic resonance techniques. In addition, potential energy calculations aimed at studying the conformation of the side chain have been performed on isolated molecules and on molecules in the crystal.

Results and discussion

Isomerism/tautomerism in the crystal state

Single crystals of two representative members of the compounds under investigation, *i.e.* **5** and **6**, have been submitted to X-ray crystallography. Their molecular structures are depicted

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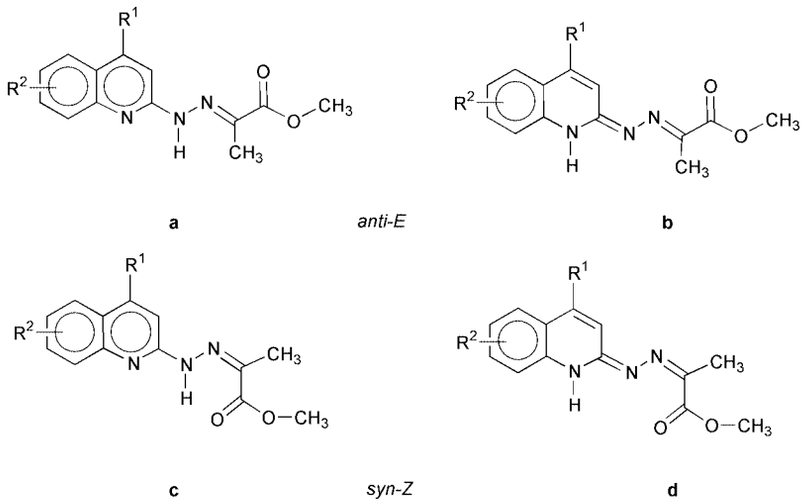

Scheme 2

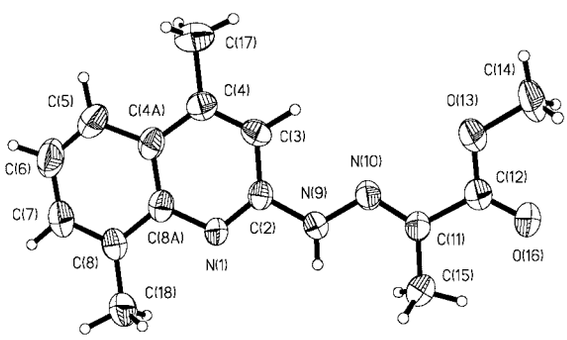

Fig. 1 Drawing of the molecular structure of compound **5**. The non-H displacement ellipsoids enclose 50% probability.

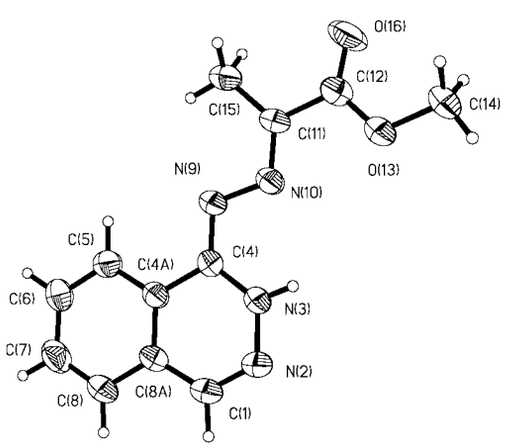

Fig. 2 Drawing of the molecular structure of compound **6**. The non-H displacement ellipsoids enclose 50% probability.

in Figs. 1 and 2, respectively, while selected bond lengths and angles are compared in Table 1.

In **5**, the distances N(1)–C(2) and N(1)–C(8A) of the quinoline ring are not equal, the latter being considerably longer, in agreement with previously published data.[15,16] The heterocycle is planar with the two methyl carbon atoms deviating 0.078(8) (C(17)) and 0.136(8) Å (C(18)) from its plane.

The data show that **5** has the *anti-E* configuration. Between the two possible tautomers, the mobile proton resides on the hydrazone nitrogen N(9). The distances C(2)–N(9) and N(9)–N(10) are equal to 1.402(5) and 1.351(5) Å, respectively. The former value is slightly longer than the corresponding distances (1.372(4)–1.376(3) Å) determined in quinolylhydrazones derived from thiophenecarbaldehydes.[9]

Table 1 Selected bond lengths (Å) and angles (°) for **5** and **6**

5		**6**	
N(1)–C(2)	1.310(5)	N(9)–N(10)	1.398(4)
N(1)–C(8A)	1.372(5)	C(11)–C(12)	1.488(5)
C(11)–C(12)	1.491(6)	C(11)–C(15)	1.491(5)
C(11)–C(15)	1.503(6)	C(12)–O(13)	1.333(4)
C(12)–O(13)	1.324(6)	O(13)–C(14)	1.448(5)
O(13)–C(14)	1.456(6)		
N(1)–C(2)–N(9)	113.0(3)	C(1)–N(2)–N(3)	116.5(3)
C(2)–N(9)–N(10)	121.3(3)	C(4)–N(9)–N(10)	110.4(3)
N(9)–N(10)–C(11)	116.5(3)	N(9)–N(10)–C(11)	113.7(3)
N(10)–C(11)–C(15)	125.4(4)	N(10)–C(11)–C(15)	125.9(3)
C(11)–C(12)–O(13)	113.9(4)	C(11)–C(12)–O(13)	115.1(3)

In **6**, the distance C(1)–N(2) is equal to 1.289(5) Å, clearly indicating its double bond nature. The bond lengths N(2)–N(3), N(3)–C(4), and C(4)–N(9) are equal to 1.373(5), 1.357(4), and 1.319(5) Å, respectively. These data suggest a single bond between the endocyclic nitrogen atoms N(2) and N(3), while a double bond is assigned to C(4)–N(9). In the final stage of the refinement a hydrogen atom was located to 0.874(3) Å from N(3), confirming this assumption. It follows that, unlike **5**, the molecular structure of **6** corresponds to the imino tautomer in which the hydrogen is located at the endocyclic nitrogen N(3) (Fig. 2). To the best of our knowledge, it is the first case of an X-ray structure of a neutral phthalazinylhydrazone with the mobile hydrogen located at an endocyclic position. Similarly to its quinoline derivative, phthalazinylhydrazone **6** has an *anti-E* configuration (Fig. 2).

Several crystal structures of mono- and biprotonated hydrazinophthalazine derivatives have been reported. The crystal structure of 1-hydrazinophthalazine hydrochloride shows that one acidic proton resides on the endocyclic N(2) and the other on one nitrogen of the pendant hydrazine residue.[17,18] Similarly, the crystal structures of protonated 1,4-dihydrazinophthalazines show the same arrangement of the two acidic protons.[19–21] On the other hand, in 1,4-bis(2′-pyridiniomethylenehydrazino)phthalazine nitrate dihydrate the acidic proton resides on the exocyclic nitrogen.[22]

In **6** the values of endocyclic bond angles are regular and in agreement with those found in analogous hydrazinophthalazine derivatives. The heterocycle is planar. C(4) shows the largest deviation (0.027(3) Å) from the plane. The distance N(10)–C(11) is equal to 1.291(5) Å, very close to the value of 1.284(6) Å found in **5** and in other analogous derivatives.[22] The bond angle C(4)–N(9)–N(10) is equal to 110.4(3)°, a slightly low value in comparison with that found in the phthalazin-1(2*H*)-

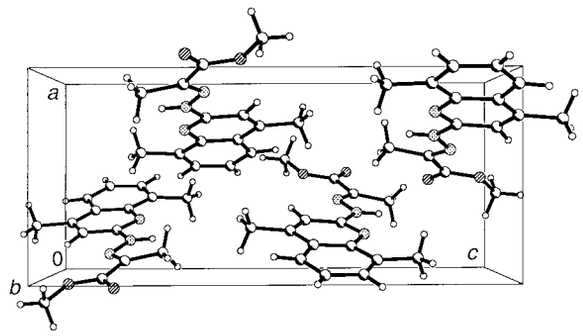

Fig. 3 Crystal packing of compound **5** viewed along the *b* axis.

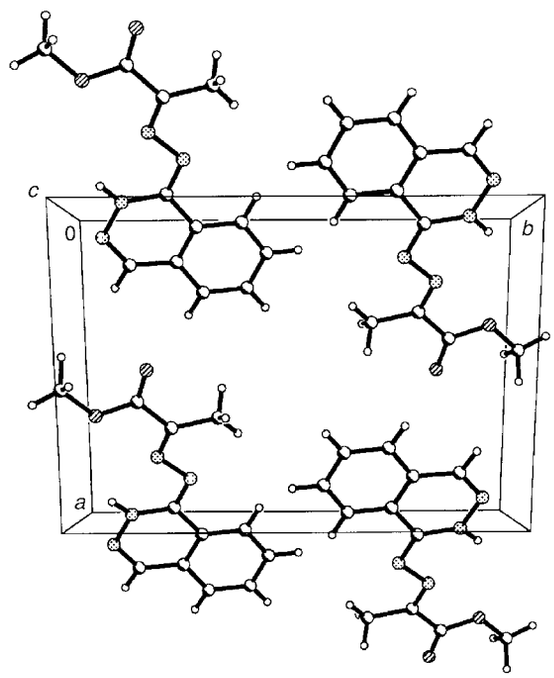

Fig. 4 Crystal packing of phthalazinylhydrazone **6** viewed along the *c* axis.

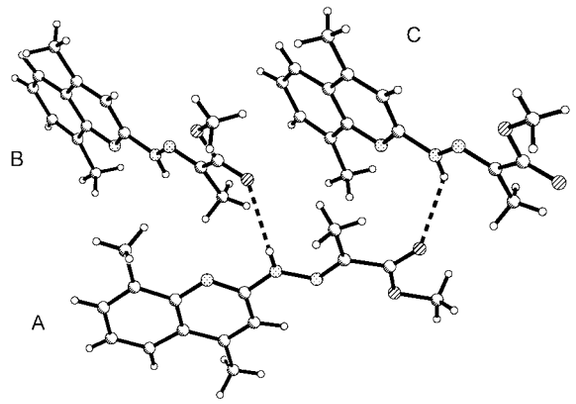

Fig. 5 Intermolecular hydrogen bonds occurring in the crystal lattice of **5**. Symmetry codes: A: x, y, z; B: $-x, -\frac{1}{2}+y, \frac{1}{2}-z$; C: $-x, \frac{1}{2}+y, \frac{1}{2}-z$.

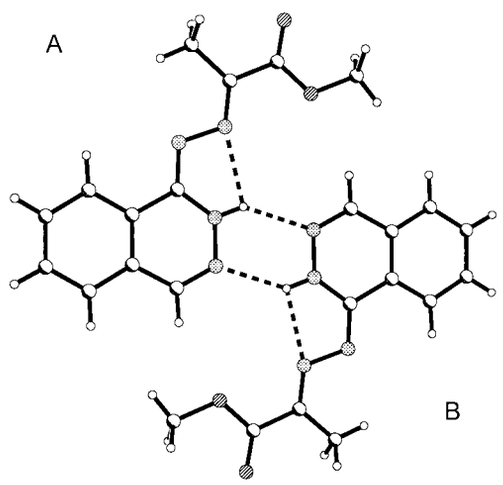

Fig. 6 Base pair of the phthalazine rings in compound **6**. Intra- and intermolecular hydrogen bonds are shown by dashed lines. Symmetry codes: A: x, y, z; B: $2-x, 1-y, -z$.

one hydrazone hydrochloride (119.8(3)°)[18] or in 1,4-dihydrazinophthalazinium derivatives (mean value = 117.5(4)°).[20–22]

In both compounds the aliphatic hydrazone substituent is planar. The dihedral angle with the heterocycle is equal to 8.1(1)° (**5**) and 3.9(1)° (**6**).

The presence of different tautomers influences the supramolecular chemistry of **5** and **6**, and in particular their crystal packings (Figs. 3, 4). Both are stabilized by van der Waals and hydrogen bonding interactions.

In particular, each molecule of **5** participates in N–H···O hydrogen bonding with two other molecules through the pairwise interactions O(16)···H–N(9) ($-x, \frac{1}{2}+y, \frac{1}{2}-z$) and N(9)–H···O(16) ($-x, -\frac{1}{2}+y, \frac{1}{2}-z$) with the distances O···H, O···N and the O···H–N angle equal to 2.397(3), 3.070(5) Å and 133.8(2)°, respectively (Fig. 5). On the other hand, the side chain of **6** does not participate in hydrogen bonding interactions. In this case there is a three-centred hydrogen bond consisting of two interactions: an intramolecular one, *i.e.* N(3)–H···N(10) (distances H···N(10) and N(3)···N(10) equal to 2.319(3) and 2.573(4) Å, respectively), and an intermolecular N(3)–H···N(2) ($-x+2, 1-y, -z$) interaction in which the H···N(2) and N(3)···N(2) distances are equal to 2.192(3) and 2.926(4) Å, respectively, and the N(3)–H···N(2) angle is 141.4(2)° (Fig. 6).

The heteroaromaticity index (I_A) for **5** is equal to 130, in agreement with previously published data.[7] As **6** is the first neutral 2*H*-phthalazine tautomer for which X-ray data are available, it is interesting to evaluate its heteroaromaticity. Its calculated I_A is equal to 127, suggesting a nearly aromatic nature of the 6,6-fused ring system. This value is significantly less than that obtained for phthalazine ($I_A = 136$)[23] and of that calculated for protonated phthalazine derivatives ($I_A = 133$–136).[21] On the other hand, it is very close to that obtained for quinolin-2-one ($I_A = 127.5$).[7] The tautomeric system phthalazine/2*H*-phthalazine shows a $\Delta I_A = 9$ and a calculated resonance energy difference[23] equal to 13.4 kJ mol^{-1}.

Isomerism/tautomerism in solution

The present investigation has been also aimed at the study of isomerism/tautomerism equilibria in solution. Different ^{1}H and ^{13}C NMR experiments have been carried out. We first consider the behaviour in deuterochloroform solution of compounds **5** and **6**, whose crystal and molecular structures have been determined.

In the case of the phthalazine **6**, only one set of ^{1}H and ^{13}C signals was observed. By irradiating the methyl singlet at 2.40 ppm an NOE effect was produced on the H(5) multiplet, confirming the presence of a single *anti-E* isomer in the solution, as it is observed in the crystal state (Tables 2, 3). Concerning its tautomeric structure, we found that in the ^{1}H spectrum the H(N) signal is shifted downfield (10.83 ppm) in respect to the other quinoline derivatives **1**–**5** (8.53–8.62 ppm). Furthermore in the ^{13}C-coupled spectrum the C(1) resonates as a ddd, due to its coupling with three different hydrogens, *i.e.* H(1), H(8) and the proton on the nitrogen in the 3-position.

Table 2 ^{13}C data (δ/ppm) of the quinolines **1**–**5** and phthalazine **6** (solvent: deuterochloroform)

Compound	**1**	**2**	**3**	**4**	**5**	**6**
C(2)	154.5	154.1	153.5	154.6	153.2	139.1 (C(1))
C(3)	110.0	109.9	109.9	107.6	109.5	—
C(4)	138.7	147.2[a]	146.6[a]	147.1[a]	147.3[a]	150.0
C(5)	127.8[a]	124.0	123.2	125.2	121.8	125.0
C(6)	124.2	124.0	123.5	116.2	123.4	131.9[a]
C(7)	130.2	129.8	131.8	124.5	129.9	132.7[a]
C(8)	126.7[a]	127.1	126.9	106.0	135.1	126.1
C(4A)	125.7	125.9	125.8	120.7	125.6	127.6[b]
C(8A)	146.8	146.7[a]	145.0[a]	148.6[a]	145.7[a]	126.5[b]
Other signals	10.9 (Me); 52.5 (OMe); 135.1 (C=N); 165.3 (CO)	11.8, 19.9 (Me); 53.5 (OMe); 134.8 (C=N); 165.3 (CO)	10.8, 19.1, 21.6 (Me); 52.5 (OMe); 134.4 (C=N); 165.2 (CO)	10.8, 19.0 (Me); 52.6, 55.4 (OMe); 134.8 (C=N); 161.2 (CO)	10.8, 18.2, 19.3 (Me); 52.5 (OMe); 134.2 (C=N); 165.4 (CO)	13.4 (Me); 52.3 (OMe); 151.6 (C=N); 166.1 (CO)

[a] Assignment may be reversed. [b] Assignment may be reversed.

Table 3 ^{1}H NMR data (δ/ppm (J/Hz)) of the quinolines[a] **1**–**5** and phthalazine **6** (solvent: deuterochloroform)

Compound	**1**	**2**	**3**	**4**	**5**	**6**
H(3)	7.74d (7.5)	7.59s	7.59s	7.44s	7.58s	7.98s (H(1))
H(4)	8.11d (9.1)	—	—	—	—	—
H(5)	obscured	7.89d (8.3)	7.64d (1.1)	7.81d (8.8)	7.72d (7.8)	8.49m
H(6)	7.37td (7.2, 1.3)	7.40dd (8.3, 7.2)	—	7.02dd (8.8, 2.3)	7.23t (7.8)	7.70m
H(7)	7.64td (6.9, 1.3)	7.63dd (8.3, 7.2)	7.46dd (7.0, 1.1)	—	7.48d (7.0)	7.70m
H(8)	obscured	7.77d (8.3)	7.64d (7.0)	7.12d (2.3)	—	7.51m
NH	8.62br	8.53br	8.55br	8.56br	8.61br	10.83br
OMe	3.88s	3.89s	3.93s	3.91s, 3.93s	3.90s	3.89s
Me	2.18s	2.17s	2.18s	2.19s	2.20s	2.40s
Ar-Me	—	2.70d (1.0)	2.53s, 2.72s	2.68s	2.68s, 2.72s	—

[a] Minor signals, due to *Z* isomer and/or tautomers are also present.

These data indicate that the imino tautomeric form is present both in the crystal state and in chloroform solution. This isomeric/tautomeric structure remains unaltered from room temperature to −60 °C, where coalescence phenomena or new sets of signals were not observed. This is interesting because analogous compounds, such as 1-aminophthalazine, mainly exist in the amino tautomeric form,[24] suggesting that the electron distribution in the side chain of **6** plays an important role in stabilizing the imino tautomer.

A different situation is observed for the quinoline derivative **5**. In deuterochloroform solution, in addition to the main ^{1}H and ^{13}C NMR signals (Tables 2, 3), confirming its aromatic *anti-E* configuration, a further set of signals with relative intensity about 3% in respect to the most abundant ones is present [^{1}H: 2.34, 2.46, 2.48 (Me), 3.88 (OMe), 6.74, 7.12 (CH), 10.06 (NH) ppm; ^{13}C: 13.2, 16.1, 42.5 (Me, OMe), 119.1, 122.7, 131.8 (CH) ppm]. Performing NOE experiments, owing to saturation of the intense singlet at 7.58 ppm (H(3)), the small singlet at 6.74 ppm disappears, as a consequence of a chemical exchange equilibrium between two compounds. As the singlet at 6.74 ppm is due to H(3) experiencing a non-aromatic heterocyclic system, we can conclude that the minor set of signals is attributable to the imino tautomer (structure **b**, Scheme 2). On the other hand, in DMSO-d_6 solution only one set of signals is detectable, indicating the presence of only the full aromatic tautomer or faster interconversion of the two tautomers in this solvent.

A similar situation was found for the other quinoline derivatives **1**–**4**. For all of them, the most abundant structures correspond to the amino *anti-E* isomers. Similarly to the derivative **5**, for compounds **2** and **3** a minor set of signals, attributable to the imino tautomer on the basis of the H(3) signal at 6.7 ppm, is detectable in deuterochloroform solution. On the other hand, **1** and **4** are in the amino form only. In addition, for the quinolines **1**–**4** we found a further set of signals with relative intensities in the range 3–8%. As an example, compound **3** shows four singlets at 2.22, 2.55, 2.68 (Me) and 3.85 (OMe) ppm that can be reasonably assigned to the presence, in the reaction mixture, of a small amount of the corresponding amino *syn-Z* isomer (structure **c**, Scheme 2).

Molecular conformation

After having determined the isomerism/tautomerism of hydrazone derivatives **1**–**6**, our attention has been devoted to their conformation. In fact the hydrazone side chain may show a wide extent of rotational freedom. Therefore it might assume a lot of different conformations.

To evaluate the energy barriers associated with the rotations around the bonds N(9)–N(10) and C(11)–C(12) in **5** and in **6**, van der Waals potential energy calculations have been carried out on isolated molecules as well as on molecules in the crystal. The molecular structures of **5** and **6** determined by the X-ray data were used as starting geometries.

The data show that the two compounds have quite similar potential energy profiles, but both with large differences between an isolated molecule and a molecule in the crystal. In the isolated molecules of **5** and **6**, the rotation of the torsion angle N(10)–C(11)–C(12)–O(16) does not involve severe steric hindrance over all the −180–180° range, with energy minima calculated around ±80° for both compounds. On the other hand, when calculations are carried out on the molecules in the crystal lattice a wide range of rotation becomes forbidden owing to too short intermolecular interactions (Fig. 7, top). For both **5** and **6** the energy minima are calculated at values very close to those found in the X-ray structures (178.0(4) (**5**) and 172.5(3)° (**6**)).

The rotation around the torsion angles C(2)–N(9)–N(10)–C(11) and C(4)–N(9)–N(10)–C(11) in the isolated molecules of **5** and **6**, respectively, has a narrower range of freedom with

minima in the regions around ±110° (Fig. 7, bottom). Values of the torsion angles encompassed between −60 and 60° are not allowed owing to intramolecular steric hindrance mainly due to the methyl groups on the hydrazone side chain. When calculations are performed on the molecules in the crystal lattice, the calculated minima are calculated at the same values determined by X-ray crystallography (−175.3(4) (**5**) and −176.4(3)° (**6**)).

These data suggest that intermolecular interactions present in the crystal lattice play a driving role in determining the conformation of the hydrazone side chain, so that only a very narrow range of conformational freedom is calculated to be possible for the molecules in the crystal.

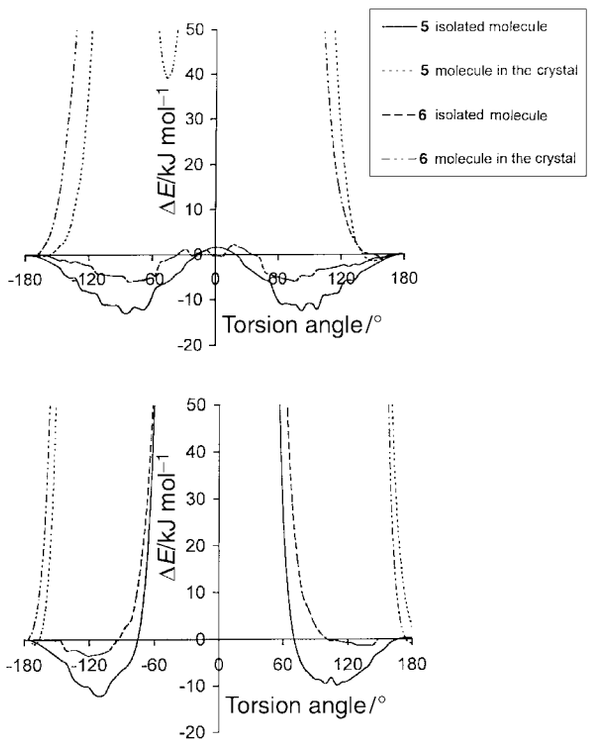

Fig. 7 Calculated potential energy profiles (ΔE/kJ mol^{-1}) for the rotation of the torsion angles N(10)–C(11)–C(12)–O(16) (top) and C(2)/C(4)–N(9)–N(10)–C(11) (bottom) in the isolated molecules and in the crystal lattices of **5** and **6**.

Conclusions

The present study has allowed us to obtain useful information on isomerism/tautomerism of α-N-heterocyclic hydrazones both in the crystal state, in solution, and on their conformational properties.

In the crystal state the quinoline derivative **5** corresponds to the amino *anti-E* isomer. This occurs also in solution for all the quinolines **1**–**5**, even if other tautomerism/isomerism equilibria are present to a lesser extent. On the contrary, the phthalazinylhydrazone **6** corresponds to the imino *anti-E* isomer, both in the crystal state and in solution where other isomeric/tautomeric species are not detectable. The different locations of the acidic hydrogen in the quinoline and phthalazine derivatives produce quite large differences in their intermolecular interactions occurring in the crystal lattice. The conformation of the hydrazone side chain is quite similar in the X-ray structures, and also in the results from calculations.

As the compounds have the same side chain, this study has shown that two main factors play a key role in stabilizing a given tautomer and isomer: *i.* the nature of the heterocycle and its electronic distribution, *ii.* intermolecular interactions, and in particular hydrogen bonding network and van der Waals interactions.

This study produced detailed information on isomerism/tautomerism of α-N-heterocyclic hydrazones that can also be useful in drug design and in the design of new chelating agents.

Experimental

Synthesis of the compounds

α-N-Heterocyclic hydrazones **1**–**6** were prepared by the reaction between the corresponding α-N-hydrazino derivative with methyl pyruvate or pyruvaldehyde in ethanolic or methanolic solutions according to previously reported procedures.[13] Single crystals of **5** and **6** were obtained by dissolving 50 mg of powder of each compound in 50 ml methanol and allowing the solution to concentrate at room temperature.

Table 4 Crystal data for 2-[(4,8-dimethylquinolin-2-yl)hydrazono]propionic acid methyl ester (**5**) and 2-[(1,2-dihydrophthalazin-1-ylidene)-hydrazono]propionic acid methyl ester (**6**)

	5	**6**
Formula	$C_{15}H_{17}N_3O_2$	$C_{12}H_{12}N_4O_2$
M	271.32	244.26
Crystal size/(mm)	0.20 × 0.25 × 0.40	0.10 × 0.25 × 0.20
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$ (no. 19)	$P2_1/c$ (no. 14)
a/Å	7.828(1)	10.235(1)
b/Å	10.223(1)	13.717(2)
c/Å	17.783(2)	8.895(1)
β/°		111.00(1)
U/Å^3	1410.3(3)	1165.9(2)
Temperature/K	293	293
Z	4	4
F(000)	576	512
D_c/g cm^{-3}	1.278	1.392
μ(Mo-Kα)/mm^{-1}	0.9	1.0
Scan mode	ω	ω
Scan range/°	$1 \leq \theta \leq 25$	$1 \leq \theta \leq 25$
Scan width/°	0.96	1.06
Scan speed/° min^{-1}	337.2 exp(−3.08 sin θ/λ)^2	2.1
Independent reflections	1810 (R_{int} = 0.012)	2050 (R_{int} = 0.075)
Obs. reflections ($I > 2\sigma(I)$)	1052	978
No. parameters refined	186	161
R_1 ($I > 2\sigma(I)$)	0.054	0.058
wR_2 ($I > 2\sigma(I)$)	0.095	0.092

X-Ray crystal structure determinations †

Crystal data for compounds **5** and **6** are reported in Table 4. A Siemens P4 four-circle diffractometer with graphite monochromated Mo-Kα radiation was used for data collection. Both crystal structures were solved and refined, by full-matrix anisotropic least-squares on F^2 for all reflections for all non-H atoms, by using SHELX-97.[25] Compound **5** crystallizes in an acentric space group, but owing to the presence of only light atoms, the absolute structure could not be determined reliably.

Geometrical calculations and molecular graphics were performed by using PARST96[26] and SHELXTL[27] packages, respectively.

Nuclear magnetic resonance

The ^{1}H and ^{13}C NMR spectra were recorded at 200.13 and 50.33 MHz respectively with a Bruker AC 200 instrument. NOE experiments were carried out using the NOEDIFF pulse sequence.

Non-bonded potential energy calculations

Atom–atom non-bonded potential energy calculations were carried out by using the function: $E_{jk} = B_{jk} \exp(-C_{jk}\ r_{jk}) - A_{jk}\ r_{jk}^{-6}$ implemented in the program ROTENER.[28] The X-ray structures of **5** and **6** were used as starting geometries. The torsion angles N(10)–C(11)–C(12)–O(16) (**5**, **6**), and C(2)–N(9)–N(10)–C(11) (**5**), and C(4)–N(9)–N(10)–C(11) (**6**), were rotated by steps of 5° in the range −180–180° both in isolated molecules and in molecules in the crystal lattice.

† CCDC reference number 188/269. See http://www.rsc.org/suppdata/p2/b0/b004448m/ for crystallographic files in .cif format.

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