The Structures of Indazolin-3-one (= 1,2-Dihydro-3*H*-indazol-3-one) and 7-Nitroindazolin-3-one

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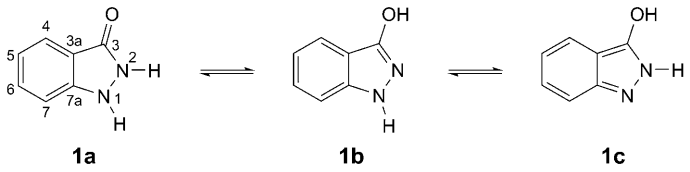
In memoriam Professor *Robert Jacquier* of the University of Montpellier (France)

The existence of polymorphism in parent indazolin-3-one (= 1,2-dihydro-3*H*-indazol-3-one; **1**) is reported as well as an X-ray and NMR CPMAS study establishing that its 7-nitro derivative **2** exists as the 3-hydroxy tautomer. Absolute shieldings calculated at the GIAO/B3LYP/6-311++G(d,p) level were used to determine the tautomeric oxo/hydroxy equilibrium in solution, *i.e.*, always the 1*H*-indazol-3-ol tautomer predominates.

Introduction. – In 1986, we published a paper where the tautomerism of indazolin-3-one (**1**; 1,2-dihydro-3*H*-indazol-3-one; *Scheme 1*) was studied by X-ray crystallography and by ^{13}C- and ^{15}N-NMR both in solution and ^{13}C-NMR in the solid state [1]. The main conclusions of this study were that in the solid state, only tautomer **1a** was present, while in (D_6)DMSO, 85% of **1b** and 15% of **1a** coexist. Other authors found at the same time and in the same solvent 75 ± 3% of **1b** and 25 ± 3% of **1a** [2]. This result is somewhat surprising since in general, the tautomer found in the solid state coincides with the most abundant tautomer in solution [3].

Scheme 1. *Three tautomers of indazolinone* **1**



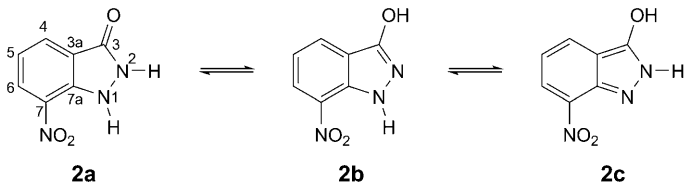
1a **1b** **1c**

After this article was published, the interest on indazolinone **1** remained unabated. Its main biological significance is related to neuronal nitric oxide synthase (nNOS) and kinase inhibitors [4]. Four papers have been published on the tautomerism of **1** [5–8].

A paper on the phototautomerization of **1** concludes that the enol **1b** dominates in nonpolar solvents and the keto form **1a** in polar and H-bonding solvents, *e.g.*, H_2O [5]. This is in agreement with a very careful study based on pK_a determinations, that reached the conclusion that in H_2O, 95% of **1a** and 5% of **1b** are present [6]. When included in a cyclodextrine, the tautomer present is **1b** [7]. Finally, *Matos* and coworkers published an experimental and computational thermochemistry study of indazolin-3-one [8]. This last work reports not only a standard enthalpy of formation of 70.0 ± 2.2 kJ mol^{-1} but theoretical calculations of the tautomeric equilibrium (a positive sign means that tautomer **1b** is the most stable): 7.90 (B3LYP/6-31G*), 3.46 (B3LYP/6-311G**), -0.09 (B3LYP/cc-pVTZ), and -17.98 (MP2/cc-pVTZ) showing enormous dispersion. For this reason alone, the tautomerism of indazolin-3-one deserved to be revisited. Besides, there is interest in the synthesis and reactivity of indazolin-3-one (**1**) [9–11] and mainly in its biological properties [12][13]. A search in the *Cambridge Structural Database* [14] shows that no other structure of N(1),N(2)-unsubstituted indazolin-3-ones other than that of **1** (refcode FADMIG) has been published.

In this article, we will examine again indazolinone **1** together with its 7-nitro derivative **2** (*Scheme 2*). We have prepared compound **2** within a study program of inhibitors of the NOS (nitric oxide synthase), where 7-nitroindazole was an active compound [15–18]. All nitroindazolinones are known compounds [19][20], but while the 5-nitro isomer is rather common and the 6-nitro has been described several times, a search in the *Chemical Abstracts* for the 7-nitro isomer **2** (CAS 31775-97-0) between 1987 and 2008 afforded only two patents [12][21]. Furthermore, nothing is known about the tautomerism of compound **2**.

Scheme 2. *Three tautomers of 7-nitroindazolinone* **2**



2a **2b** **2c**

Results and Discussion. – *Theoretical Calculations: Energies and Absolute Shieldings.* We carried out B3LYP/6-311++G(d,p) calculations (see *Exper. Part*) of the six molecules of *Schemes 1* and *2*. We used the optimized geometries (no imaginary frequencies) to calculate the corresponding absolute shieldings (σ, GIAO), and we transformed σ into chemical shifts δ by means of *Eqns. 1–3* (only ^{1}H, ^{13}C and ^{15}N because we have no data on ^{17}O) that were obtained by fitting computed shieldings and experimental chemical shifts [22]:

$$\delta(^1\mathrm{H}) = 31.0 - 0.97\ \sigma(^1\mathrm{H}) \quad (1)$$

$$\delta(^{13}\mathrm{C}) = 175.7 - 0.963\ \sigma(^{13}\mathrm{C}) \quad (2)$$

$$\delta(^{15}\mathrm{N}) = -148.0 - 0.95\ \sigma(^{15}\mathrm{N}) \quad (3)$$

Concerning the energies, in the case of **1**, the minimum is **1b** (−455.194294 hartree) followed by **1a** (24.0 kJ mol^{-1}), and the least stable is **1c** (41.2 kJ mol^{-1}). In the 7-nitro series, the minimum is also the 1*H*-indazol-3-ol derivative **2b** (−659.76173 hartree), then **2a** (5.1 kJ mol^{-1}) and **2c** (70.4 kJ mol^{-1}). Although the ordering is the same, in the gas phase, the 7-nitro group stabilizes the indazolinone **2a** and destabilizes the 2*H*-indazol-3-ol **2c**. The dipole moments [D] are: 5.48 (**1a**), 1.72 (**1b**), 2.94 (**1c**), 0.97 (**2a**), 3.84 (**2b**), and 8.28 (**2c**). The chemical shifts are reported in *Table 1*.

Table 1. *GIAO-Calculated ^{1}H-, ^{13}C-, and ^{15}N-NMR Chemical Shifts δ*

	1a	**1b**	**1c**	**2a**	**2b**	**2c**
N(1)	−284.34	−234.25	−121.91	−266.16	−223.00	−114.22
N(2)	−241.41	−116.82	−195.53	−233.09	−110.56	−189.85
N(7) (NO_2)	–	–	–	−12.03	−11.26	−14.21
C(3)	154.85	154.32	143.88	162.28	155.10	146.22
C(3a)	115.69	111.96	104.89	121.90	115.45	108.98
C(4)	125.68	120.50	115.12	132.89	129.18	123.91
C(5)	117.59	118.80	119.48	119.32	117.70	116.95
C(6)	131.34	127.04	125.75	128.86	125.21	127.44
C(7)	105.23	107.06	120.03	134.80	132.93	139.59
C(7a)	140.59	141.73	149.04	144.61	134.99	140.91
H−N(1)	6.07	7.69	–	7.52	9.61	–
H−N(2)	6.79	–	9.02	6.28	–	9.26
OH	–	4.83	4.43	–	5.02	4.81
H−C(4)	7.89	7.72	7.15	8.11	7.98	7.50
H−C(5)	6.81	7.00	6.83	7.05	7.04	6.90
H−C(6)	7.28	7.27	7.14	8.29	8.27	8.50
H−C(7)	6.69	7.06	7.57	–	–	–

The Case of Indazolinone **1**. In *Table 2*, the experimental results concerning indazolinone **1** are given. The chemical shifts of **1** were reported previously [1]. In the solid state, they correspond to tautomer **1a** whose structure was determined by X-ray crystallography. When recording the CPMAS (cross-polarization magic-angle spinning) spectra of a commercial sample of **1** (*Aldrich 12606*, 97%) we discovered another polymorph. Some signals (of both N-atoms and of C(3), C(3a), and C(7a)) were splitted (see *Fig. 1*). Using two solvents, we succeeded in obtaining pure polymorph I (in EtOH) and polymorph II (in AcOEt). The NMR chemical shifts of the solid compound we described in our 1986 paper (see *Table 2*) correspond to polymorph I (it was obtained from a MeOH solution) [1].

We excluded that it is a case of desmotropy (two different tautomers). Comparison of the experimental data (*Table 2*) with the calculated ones for the three tautomers (*Table 1*) clearly shows that both samples are polymorphs of the same tautomer **1a** (we included the references at δ 0.0 in the regressions) (*Eqns. 4* and *5*). The square correlation coefficients R^2 for calculated **1b** and **1c** are 0.975 and 0.952 (the same for both polymorphs).

$$\delta_{\text{polymorph I}} = (9.4 \pm 1.7) + (0.93 \pm 0.01)\ \delta_{\text{calc.}}\ \mathbf{1a},\ n = 10,\ R^2 = 0.999 \quad (4)$$

$$\delta_{\text{polymorph II}} = (9.1 \pm 2.2) + (0.94 \pm 0.01)\ \delta_{\text{calc.}}\ \mathbf{1a},\ n = 10,\ R^2 = 0.998 \quad (5)$$

Table 2. *Experimental ^1H-, ^{13}C-, and ^{15}N-NMR Chemical Shifts δ of Indazolinone* **1**

	CPMAS			(D_6)DMSO	(D_{18})HMPA
	[1]	polymorph I	polymorph II		
N(1)	–	−254.0	−256.5	−234.0	−226.1
N(2)	–	−213.3	−215.9	−138.1	n.o.
C(3)	160.8	160.2	165.6	156.1	155.9
C(3a)	114.0	113.1	110.3	112.6	113.1
C(4)	123.8	121.6	121.6	120.2	120.5 ($^1J = 160.5$, $^3J = 7.3$)
C(5)	120.3	119.7	119.7	118.7	117.2 ($^1J = 158.7$, $^3J = 6.6$)
C(6)	131.6	130.5	130.5	127.3	125.6 ($^1J = 157.1$, $^3J = 7.3$)
C(7)	111.4	113.1	113.1	110.3	110.0 ($^1J = 161.5$, $^3J = 7.6$)
C(7a)	144.3	143.2	146.6	142.5	142.5
H−N(1)/*H*−N(2)	–	–	–	11.29 (br.)	12.27 (br.)
OH	–	–	–	10.55 (vbr.)	11.0 (br.)
H−C(4)	–	–	–	7.61 (*d*)	7.69 (*d*)
H−C(5)	–	–	–	6.96 (*t*)	6.80 (*t*)
H−C(6)	–	–	–	7.28 (*m*)	7.14 (*dd*)
H−C(7)	–	–	–	7.28 (*m*)	7.18 (*dd*)

In (D_6)DMSO solution, we estimated that 85% of **1b** and 15% of **1a** are present using model compounds as fixed tautomers (replacing NH and OH by MeN and MeO) [1]. Now with the calculated values of *Table 1*, the best fit was obtained for 80% of **1b** and 20% of **1a** ($n = 10$, $R^2 = 0.9998$). Remember that other authors found 75 ± 3% of **1b** and 25 ± 3 of **1a** in (D_6)DMSO [2].

The ^{1}H-NMR chemical shifts are of minor use because the most interesting ones, the NH and OH, are too dependent on specific (*i.e.*, H-bonds) and general interactions with the solvent.

When we failed to obtain suitable crystals to determine the X-ray structure of the second polymorph, we decided to generate the powder-diffraction diagram of the determined polymorph (FADMIG) and to record the powder diffractograms of both polymorphs (*Fig. 2*). To our surprise, the already determined structure (FADMIG) corresponds to polymorph II! We then realized that the X-ray structure was determined from a crystal obtained by leaving a saturated solution in DMSO to stand at room temperature (the product being insoluble in H_2O), while the ^{13}C-NMR CPMAS chemical shifts were measured from a compound purified by crystallization in MeOH.

The conclusion is that in 1986, we have already obtained both polymorphs: I in MeOH and II in DMSO but we were not aware of it.

The Case of 7-Nitroindazolinone **2**. In the case of **2**, we also succeeded in determining its molecular structure: it corresponds to the 1*H*-indazol-3-ol tautomer **2b**. Here, this tautomer is the most stable according to the calculations.

The X-ray diffraction analysis of suitable crystals of **2**, obtained from EtOH, shows that the molecule is planar including the NO_2 group in the plane (*Fig. 3*), and selected bond lengths, angles, and H-bond features are collected in *Table 3*. As expected, the distances show the N=O bond delocalization for the nitro group.

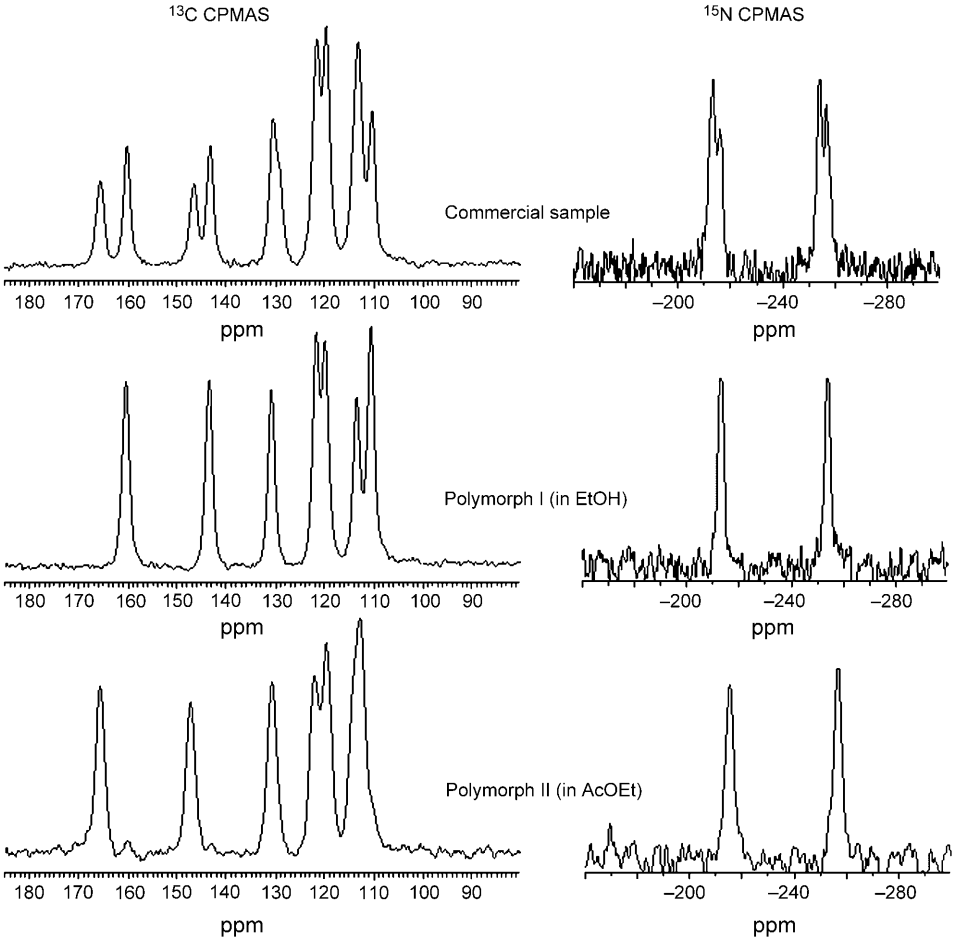


Fig. 1. *^{13}C- and ^{15}N-NMR CPMAS Spectra of compound* **1**

The molecule presents H-bonds with the surrounding molecules as depicted in *Fig. 4:* a strong one (O(1)–H(1A)···N(2′)) forming dimers linked through a weaker H-bond interaction (N(1)–H(1B)···O(2′)) that gives rise to independent layers parallel to the (1 0 1) plane.

According to the NMR data of *Table 4*, the compound in the solid state has structure **2b**, and here again, that was confirmed by the comparison of the experimental chemical shifts with the calculated ones ($n = 11$, *Tables 1* and *4*): with **2a** $R^2 = 0.984$, with **2b** $R^2 = 0.997$ (exp. $= -(4.4 \pm 2.6) + (1.04 \pm 0.02)$ calc. for **2b**), and with **2c** $R^2 = 0.907$. In solution, the best fittings were for (D_6)DMSO, 98% **2b** and 2% **2a** ($n = 14$, $R^2 = 1.000$) and for (D_{18})HMPA, 87% **2b** and 13% **2a** ($n = 11$, $R^2 = 1.000$) (HMPA = *N*,*N*,*N*,*N*′,*N*′,*N*′-hexamethylphosphoric triamide). In (D_6)DMSO, the comparison between compounds **1** and **2** shows that the nitro group increases the proportion of **b**

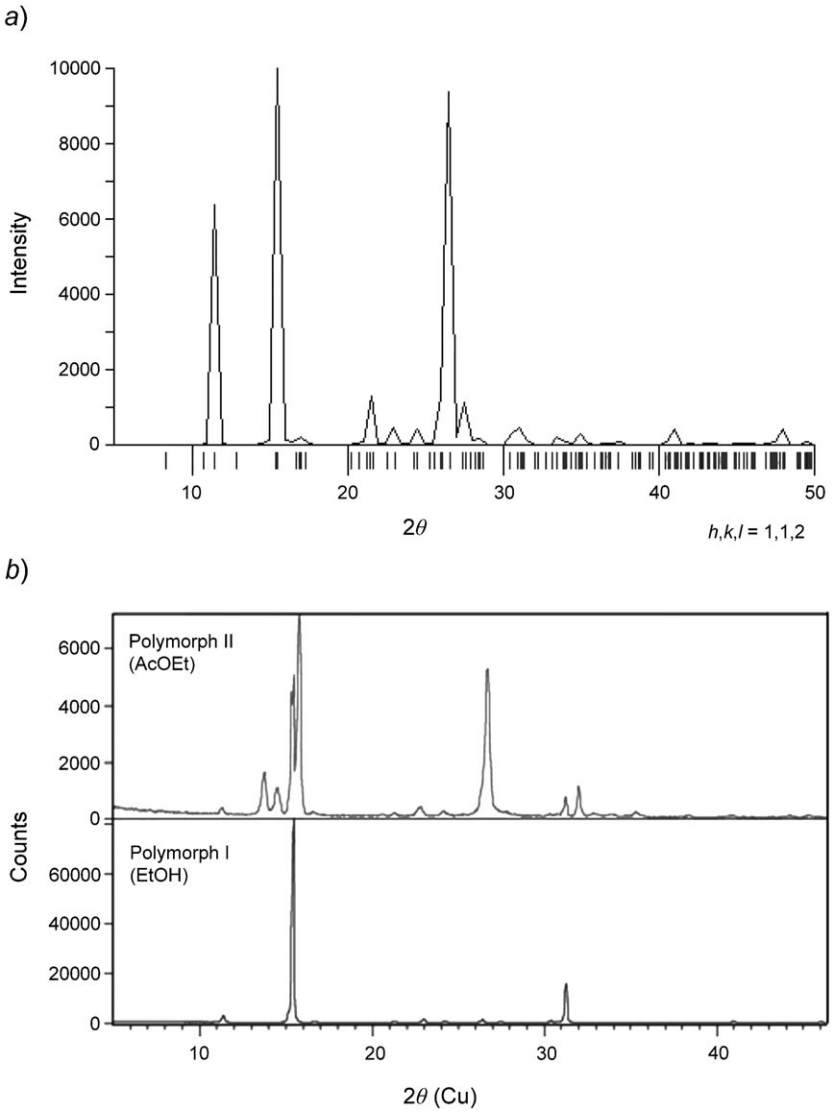


Fig. 2. a) *Calculated powder diffractogram of FAMDIG* (three main peaks at 11.5, 15.5, and 26.5 in 2θ units); b) *experimental powder diffractograms of polymorphs II* (main peaks at 11.4, 15.4, and 26.5) *and I* (main peaks at 15.5 and 31.3).

tautomer; this appears to be more related to the dipole moments than to the differences in energy.

Conclusions. – The main conclusions of this study are the final characterization of both polymorphs of indazolinone **1a** and the determination of the structure of its 7-nitro derivative as being **2b**. In (D_6)DMSO solution, both compounds show a clear

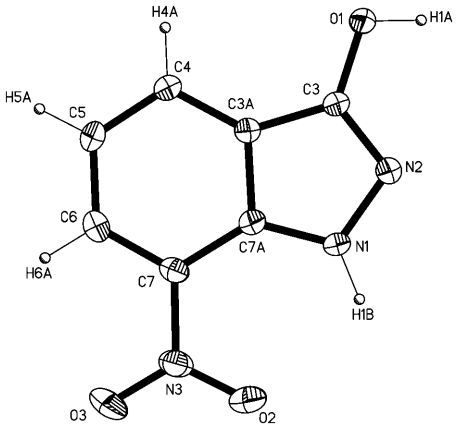


Fig. 3. *An ORTEP view* (30% probability level) *of the monomer of* **2**

Table 3. *Selected X-Ray Parameters of Compound* **2** *Including the H-Bonds.* Lengths in Å and angles in °.

N(1)–N(2)	1.385(2)	N(3)–O(3)	1.223(2)	N(1)–N(2)–C(3)	106.3(1)
N(2)–C(3)	1.312(2)	O(1)–H(1A)	0.92	N(2)–C(3)–C(3a)	111.5(1)
C(3)–C(3a)	1.425(2)	N(1)–H(1B)	0.92	C(3)–C(3a)–C(7a)	103.8(1)
C(3a)–C(7a)	1.410(2)	O(1)···N(2)[a])	2.715(2)	C(3a)–C(7a)–N(1)	107.6(1)
N(1)–C(7a)	1.346(2)	N(1)···O(2)[b])	3.047(2)	C(7a)–N(1)–N(2)	110.8(1)
C(3)–O(1)	1.335(2)	N(2)[a])···H(1A)	1.81	O(2)–N(3)–O(3)	122.5(2)
C(7)–N(3)	1.441(2)	O(2)[b])···H(1B)	2.30	O(1)–H(1A)···N(2)[a])	172.3
N(3)–O(2)	1.232(2)			N(1)–H(1B)···O(2)[b])	138.2

[a]) $-x+2,\ -y-1,\ -z+1$. [b]) $-x+3/2,\ y-1/2,\ -z+3/2$.

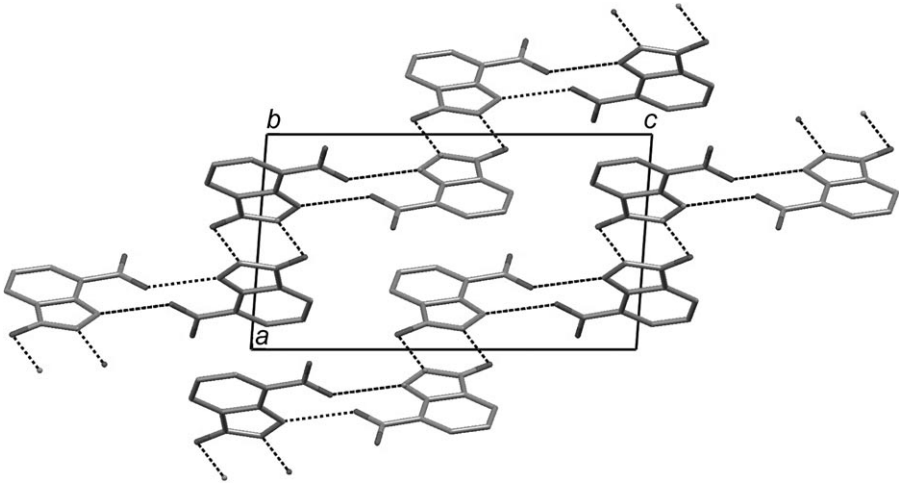


Fig. 4. *View along the* b *axis showing the H-bonds O(1)–H(1A)* ··· *N(2)*[a]) *and N(1)–H(1B)* ··· *O(2)*[b]) *in compound* **2**. The H-atoms are omitted for clarity purposes. See *Table 3* for [a])[b]).

Table 4. *Experimental ^1H-, ^{13}C-, and ^{15}N-NMR Chemical Shifts δ of 7-Nitroindazolinone* **2**. δ in ppm, J in Hz.

	CPMAS	(D_6)DMSO	(D_{18})HMPA
N(1)	– 227.7	– 221.4	–
N(2)	– 138.8	– 113.3	–
N(7) (NO_2)	– 10.1	– 10.6	–
C(3)	157.9	156.4 ($^3J = 1.8$)	157.2
C(3a)	121.9	117.1 ($^3J = 8.2$)	118.6 ($^3J = 8.0$)
C(4)	130.4	129.2 (^1J= 165.0, $^3J = 8.5$)	129.4 ($^1J = 163.1$, $^3J = 8.1$)
C(5)	116.5	118.2 ($^1J = 167.7$)	117.5 ($^1J = 166.8$)
C(6)	126.5	124.5 (^1J= 168.4, $^3J = 7.3$)	123.6 ($^1J = 164.6$, $^3J = 8.1$)
C(7)	132.1	131.3	131.9 ($^3J = 8.9$)
C(7a)	132.1	133.1 ($^3J = {}^3J = 6.8$)	133.1 ($^3J = {}^3J = 6.4$)
H–N(1), *H*–N(2)	–	12.5 (br.)	13.5 (br.)
OH	–	11.3 (br.)	11.9 (vbr.)
H–C(4)	–	8.14 (*d*, $^3J = 7.9$)	8.25 (*d*)
H–C(5)	–	7.16 (*t*)	7.27 (*t*)
H–C(6)	–	8.28 (*d*, $^3J = 7.8$)	8.26 (*d*)

predominance of the 1*H*-indazol-3-ol tautomers **b**. The 2*H*-indazol-3-ol tautomer **c** was never observed, in agreement with the DFT calculations, and also with the annular tautomerism of indazoles [3a][23–25].

The tautomerism of indazolinones not substituted at positions 1 and 2 was described as 'confused' in 1976 [26] and several years later, in 2000 [3a], the situation had not much improved save for **1**. Our work contributes to improve the situation of this important class of compounds.

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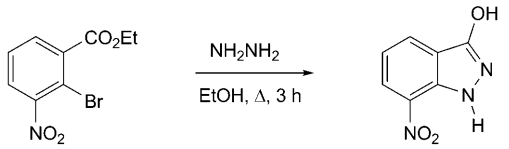
Experimental Part

1. *Synthesis of 7-Nitro-1*H-*indazol-3-ol* (**2**). Compound **2** was prepared by treating ethyl 2-bromo-3-nitrobenzoate with hydrazine in EtOH soln. (*Scheme 3*) according to [20]. Yield 84%. M.p. > 325° (EtOH; [20]: 301–305°). ^{1}H-NMR (D_6(acetone)): 11.77 (br., NH); 10.15 (br., OH); 8.34 (*d*, ^3J(4,5) = 7.9, H–C(4)); 7.28 (*t*, ^3J(4,5) = 7.9, ^3J(5,6) = 7.8, H–C(5)); 8.17 (*d*, ^3J(5,6) = 7.8, H–C(6)). ^{1}H-NMR (CD_3OD): 13.02 (br., NH); 11.35 (br., OH); 9.60 (*dd*, ^3J(4,5) = 7.9, ^4J(4,6) = 0.8, H–C(4)); 8.53 (*t*, ^3J(4,5) = 7.9, ^3J(5,6) = 7.8 H–C(5)); 9.43 (*dd*, ^3J(5,6) = 7.8, ^4J(4,6) = 0.8, H–C(6)).

2. *Calculations.* All calculations were carried out by using the B3LYP hybrid functional [27] with geometry optimization and frequencies at the B3LYP/6-31G* [28] level and a further optimization at the B3LYP/6-311++G** level [29], by using the Gaussian 03 facilities [30]. Frequency analyses were carried out at the same level used in the geometry optimizations, and the nature of the minima was determined by the absence of negative eigenvalues of the *Hessian* matrix. Using the B3LYP/6-311++G** optimized geometries, we have calculated the GIAO absolute shieldings [31].

3. *NMR Spectroscopy.* 3.1. *In Solution.* NMR Spectra: *Bruker-DRX-400* (9.4 Tesla) spectrometer; at 400.13 (^{1}H), 100.62 (^{13}C), and 40.56 MHz (^{15}N); 5 mm inverse-detection H-X probe equipped with a *z*-

Scheme 3. *Synthesis of* **2**



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gradient coil, at 300 K; chemical shifts δ in ppm from internal solvent, (D_6)DMSO δ(H) 2.49 and δ(C) 39.5, (D_6)acetone δ(H) 2.05, CD_3OD δ(H) 3.31, (D_{18})HMPA δ(H) 2.57 and δ(C) 35.82; for ^{15}N-NMR, $MeNO_2$ (δ(N) 0.00) was used as external standard. 2D (^{1}H,^{13}C) gs-HMQC, -HMBC and (^{1}H,^{15}N) gs-HMQC, and HMBC: acquired and processed by standard *Bruker* NMR software and in non-phase-sensitive mode [32].

3.2. *In the Solid State.* ^{13}C (100.73 MHz) and ^{15}N-NMR (40.60 MHz) CPMAS Spectra: *Bruker-WB-400* spectrometer; at 300 K with a 4 mm DVT probehead. Samples were carefully packed in a 4 mm diameter cylindrical zirconia rotor with *Kel-F* end caps. Operating conditions involved 3.2 µs 90° ^{1}H pulses and decoupling field strength of 78.1 kHz by TPPM sequence. ^{13}C-NMR Spectra were originally referenced to a glycine sample, and then the chemical shifts δ(C) (in ppm) were recalculated to the Me_4Si (C=O of glycine, δ(C) 176.1) and ^{15}N-NMR spectra to $^{15}NH_4Cl$ and then converted to the $MeNO_2$ scale with the relationship $\delta(N)(MeNO_2) = \delta(N)(NH_4Cl) - 338.1$. Typical acquisition parameters for ^{13}C-NMR CPMAS were: spectral width 40 kHz, recycle delay 40 s for indazolinone **1** and 10 min for 7-nitroindazolinone **2**, acquisition time 30 ms, contact time 2 ms, and spin rate 12 kHz. To distinguish protonated and unprotonated C-atoms, the NQS (non-quaternary suppression) experiment by conventional cross-polarization was recorded; before the acquisition, the decoupler was switched off for a very short time of 25 µs [33]. Typical acquisition parameters for ^{15}N-NMR CPMAS were: spectral width 40 kHz, recycle delay 40 s for indazolinone **1** and 10 min for 7-nitroindazolinone **2**, acquisition time 35 ms, contact time 6 ms, and spin rate 6 kHz.

Table 5. *Crystal Data and Structure Refinement of* **2**

Identification code	CCDC-721044	Absorption coefficient [mm^{-1}]	0.133
Empirical formula	$C_7H_5N_3O_3$	$F(000)$	368
M_r	179.14	Scan technique	ω and α
Wavelength [Å]	0.71073	θ Range [°] for data collection	3.01–27.00
Crystal system	Monoclinic	Index ranges	$-9 \le h \le 9,\ -8 \le k \le 8,\ -17 \le l \le 15$
Space group	$P2(1)/n$	Reflections collected	6184
Unit cell dimensions		Independent reflections	1673 (R(int) = 0.0470)
a [Å]	7.595(1)	Completeness to θ_{max}	99.49%
b [Å]	7.007(1)	Data, restraints, parameters	1573, 0, 118
c [Å]	13.593(1)	Goodness-of-fit on F^2	1.042
β [°]	94.223(2)	Final R^a) indices ($F^2 > 2\sigma(F^2)$)	0.041 (1079 reflections observed)
Volume [$Å^3$]	721.4(2)	wR^b) (F^2) (all data)	0.117
Z	4	Largest diff. peak and hole [$e \cdot Å^{-3}$]	0.209; −0.313
Density (calc.) [Mg/m^3]	1.649		

[a]) $\Sigma\,||F_o| - |F_c||/\Sigma|F_o|$. [b]) $\{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

4. *X-Ray Data Collection and Structure Refinement for* **2**[1]). A summary of the fundamental crystal data and refinement data of **2** is given in *Table 5*. A yellow prismatic single crystal was successfully grown from EtOH and used to collect data with a *Bruker-Smart-CCD* diffractometer with graphite-monochromated MoK_α radiation (λ 0.71073 Å) operating at 50 kV and 30 mA. The data were collected over a hemisphere of the reciprocal space by combination of three exposure sets, each exposure was of 20 s and covered 0.3° in ω. The cell parameters were determined and refined by a least-squares fit of all reflections collected. The first 100 frames were recollected at the end of the data collection to monitor crystal decay after X-ray exposition, and no important variation was observed. The structure was solved by direct methods and difference *Fourier* techniques and refined by full-matrix least-squares on F^2 (SHELXL-97) [34]. The anisotropic thermal parameters were used in the last cycles of refinement for all non-H-atoms. The H-atoms in **2** were included at their calculated positions determined by molecular geometry and refined riding on the respective C-atoms, except for the H(1A) and H(1B) atoms which were found in difference density maps, included, and refined with coordinates and thermal parameters fixed. The refinement converged to an R value of 0.041 (*Table 5*). The calculated XRD patterns were obtained with the program LAZY PULVERIX [35]. The X-ray powder diffraction was made at r.t. with a *Panalytical X'Pert PRO* α1.

REFERENCES

[1] P. Ballesteros, J. Elguero, R. M. Claramunt, R. Faure, C. Foces-Foces, F. H. Cano, A. Rousseau, *J. Chem. Soc., Perkin Trans. 2* **1986**, 1677.

[2] W. Schilf, L. Stefaniak, M. Witanowski, G. A. Webb, *Magn. Reson. Chem*. **1985**, *23*, 784.

[3] a) V. I. Minkin, A. D. Garnowskii, J. Elguero, A. R. Katritzky, O. V. Denisko, *Adv. Heterocycl. Chem*. **2000**, *76*, 157; b) I. Alkorta, J. Elguero, *J. Heterocycl. Chem*. **2001**, *38*, 1387; c) S. Trofimenko, A. L. Rheingold, L. M. Liable-Sands, R. M. Claramunt, C. López, M. D. Santa María, J. Elguero, *New J. Chem*. **2001**, *25*, 819; d) S. Trofimenko, G. P. A. Yap, F. A. Jove, R. M. Claramunt, M. A. García, M. D. Santa María, I. Alkorta, J. Elguero, *Tetrahedron* **2007**, *63*, 8104.

[4] P. A. Bland-Ward, P. K. Moore, *Life Sci*. **1995**, *57*, 131; G. Brunn, C. Hey, I. Wessler, K. Racké, *Eur. J. Pharmacol*. **1997**, *326*, 53; G. E. Demas, M. J. L. Eliason, T. M. Dawson, V. L. Dawson, L. J. Kriegsfeld, R. J. Nelson, S. H. Snyder, *Mol. Med*. **1997**, *3*, 610; G. De Sarro, P. Gareri, U. Falconi, A. De Sarro, *Eur. J. Pharmacol*. **2000**, *394*, 275; P. Pevarello, M. Villa, *Expert. Opin. Ther. Pat*. **2005**, *15*, 675.

[5] M. Krishnamurthy, S. K. Dogra, *Chem. Phys.* **1986**, *103*, 325.

[6] P. Bruneau, P. J. Taylor, A. J. Wilkinson, *J. Chem. Soc., Perkin Trans. 2* **1996**, 2263.

[7] M. Kawamura, M. Higashi, *J. Inclusion Phenom. Macrocyclic Chem*. **2005**, *51*, 11.

[8] V. M. F. Morais, M. S. Miranda, M. A. R. Matos, J. F. Liebman, *Mol. Phys.* **2006**, *104*, 325.

[9] A. Correa, I. Tellitu, E. Domínguez, R. San Martín, *Tetrahedron* **2006**, *62*, 11100.

[10] S.-L. Hu, N.-F. She, G.-D. Yin, H.-Z. Guo, A.-X. Wu, C.-L. Yang, *Tetrahedron Lett*. **2007**, *48*, 1591.

[11] A. Kiriazis, R. Rüffer, S. Jäntti, H. Lang, J. Yli-Kauhaluoma, *J. Comb. Chem*. **2007**, *9*, 263.

[12] R. T. Beresis, S. L. Colletti, to *Merck & Co*, USA, PCT Int. Appl. WO 2008051403, 2007 (*Chem. Abstr*. **2007**, *148*, 517707).

[13] J. P. Dunn, D. M. Goldstein, L. Gong, J. H. Hogg, C. Michoud, W. S. Palmer, A. Sidduri, T. Silva, P. Tivitmahaisoon, T. A. Trejo-Martin, to *F. Hoffmann-La Roche*, Switzerland, PCT Int. Appl. WO 2008068171, 2008 (*Chem. Abstr*. **2008**, *149*, 54009).

[14] CSD Database version 5.28 (November 2006), Nov 2008 update; F. H. Allen, *Acta Crystallogr., Sect. B* **2002**, *58*, 380; F. H. Allen, W. D. S. Motherwell, A*cta Crystallogr., Sect. B* **2002**, *58*, 407.

[15] C. Pérez-Medina, 'Nuevos Indazoles como inhibidores selectivos de la sintasa del óxido nítrico (NOS)', Ph.D. Thesis, UNED, Madrid, 2008.

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[1]) CCDC-721044 contains the supplementary crystallographic data of **2**. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

[16] P. Cornago, P. Cabildo, R. M. Claramunt, L. Bouissane, E. Pinilla, M. R. Torres, J. Elguero, *New J. Chem*. **2009**, *33*, 125.
[17] R. M. Claramunt, D. Sanz del Castillo, J. Elguero, P. Nioche, C. S. Raman, P. Martasek, B. S. S. Masters, 'XVIIth International Symposium on Medicinal Chemistry', Poster P101, Drugs Future, 2002, 27 (Suppl. A), 177; C. Pérez-Medina, M. Pérez-Torralba, C. López, R. M. Claramunt, P. Nioche, C. S. Raman, 'XIV Congreso Nacional de la Sociedad Española de Química Terapeútica', Bilbao, Spain, 2005.
[18] R. M. Claramunt, C. López, C. Pérez-Medina, M. Pérez Torralba, J. Elguero, G. Escames, D. Acuña-Castroviejo, *Bioorg. Med. Chem.* **2009**, *17*, 6180.
[19] K. Pfannstiel, J. Janecke, *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1096.
[20] A. J. Boulton, I. J. Fletcher, A. R. Katritzky, *J. Chem. Soc. C* **1971**, 1193.
[21] T. Hayama, K. Hayashi, M. Honma, I. Takahashi, to *Banyu Pharmaceutical Co., Ltd.*, Japan, PCT WO 2001007411, 2001 (*Chem. Abstr*. **2001**, *134*, 147614).
[22] F. Blanco, I. Alkorta, J. Elguero, *Magn. Reson. Chem*. **2007**, *45*, 797; D. Santa María, R. M. Claramunt, F. Herranz, I. Alkorta, J. Elguero, *J. Mol. Struct*. **2009**, *920*, 323.
[23] J. Catalán, J. C. del Valle, R. M. Claramunt, G. Boyer, J. Laynez, J. Gómez, P. Jiménez, F. Tomás, J. Elguero, *J. Phys. Chem*. **1994**, *98*, 10606.
[24] M. A. García, C. López, R. M. Claramunt, A. Kenz, M. Pierrot, J. Elguero, *Helv. Chim. Acta* **2002**, *85*, 2763.
[25] I. Alkorta, J. Elguero, *J. Phys. Org. Chem*. **2005**, *18*, 719.
[26] J. Elguero, C. Marzin, A. R. Katritzky, P. Linda, 'The Tautomerism of Heterocycles', Academic Press, New York, 1976.
[27] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785; A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.
[28] P. A. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213.
[29] R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.* **1971**, *54*, 724; M. J. Frisch, J. A. Pople, R. Krishnam, J. S. Binkley, *J. Chem. Phys.* **1984**, *80*, 3265.
[30] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian 03, Gaussian, Inc., Pittsburgh PA, 2003.
[31] R. Ditchfield, *Mol. Phys.* **1974**, *27*, 789; F. London, *J. Phys. Radium* **1937**, *8*, 397.
[32] S. Berger, S. Braun, '200 and More NMR Experiments', Wiley-VCH, Weinheim, 2004.
[33] S. J. Opella, D. M. H. Frey, *J. Am. Chem. Soc.* **1979**, *101*, 5855.
[34] G. M. Sheldrick, Program for Refinement of Crystal Structure, University of Göttingen, Göttingen 1997.
[35] K. Yvon, W. Jeitschko, E. Parthe, *J. Appl. Crystallogr*. **1977**, *10*, 353.

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