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Synthesis and structural study of tetrahydroindazolones

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Abstract—Multinuclear magnetic resonance spectroscopy allowed us to characterize four 1(2),5,6,7-tetrahydro-4*H*-indazol-4-one derivatives (**1**–**4**) and establish the most stable tautomer in each case. The crystal structure of 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) (orthorhombic space group $P2(1)2(1)2(1)$, $a=10.1243(8)$, $b=21.526(2)$, $c=24.992(2)$ Å, $Z=4$, 293 K) presents two different trimers, bonded through N–H···N hydrogen bonds involving tautomers 1*H* and 2*H*. In crystalline 3,6,6-trimethyl-2,5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) (monoclinic space group $P2(1)/c$, $a=5.9827(7)$, $b=16.494(2)$, $c=11.012(1)$ Å, $\beta=93.464(2)°$, $Z=4$, 293 K) only tautomer 2*H* exists forming a hydrogen-bonded network through the 4-oxo group and a water molecule.

1. Introduction

The main difference between pyrazoles **I** and their benzo derivatives, indazoles **II** (Fig. 1) is related to their annular tautomerism.[1] In pyrazoles **I**, although the tautomeric equilibrium constant depends on the nature of R^3 and R^5, it is always not very different from 1. Substituent R^4 (symmetric with regard to N1 and N2) exerts its effect through interactions with R^3 and R^5. In the case of indazoles **II**, the aromaticity of the benzene ring strongly favors the N(H)1 tautomer and only in very special cases tautomer N(H)2 becomes stable.[2]

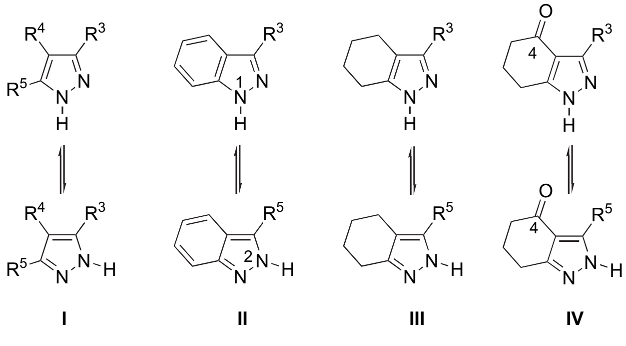

Figure 1. Structural relationships between derivatives **I**–**IV**.

If the six-membered ring is saturated, the resulting 4,5,6,7-tetrahydroindazoles **III** become again like pyrazoles [3(5),4-tetramethylenepyrazoles], both tautomers being again of similar energy.[3] The compounds that interest us now are 4-oxo derivatives **IV** of tetrahydroindazoles and therefore it is expected that, in what annular tautomerism is concerned, both tautomers would be of comparable stability.

Both pyrazoles[4,5] and indazoles[6,7] are frequently found in medicinal chemistry. Compounds **IV** have a structure intermediate between **II** and **III** because, even if the 4-hydroxy tautomer is energetically disfavored, the sp^2 hybridization at position 4 should modify the conformation of the six-membered ring.

The purpose of the present paper is twofold: (i) study the structure and tautomerism of compounds **1**–**4** belonging to the **IV** series; (ii) prepare new compounds related to indazoles for future studies as NOS inhibitors.[8–11] With these objectives, we have synthesized and characterized four 1(2),5,6,7-tetrahydro-4*H*-indazol-4-one derivatives shown in Figure 2, where the two main tautomeric forms are represented.

To approach the study of the interaction between new inhibitors and the heme catalytic domain of the endothelial isoform of NOS (eNOS),[12] it is crucial to elucidate in which tautomeric form the entitled compounds will exist. Thus, we have performed a structural study of compounds **1**–**4** to know the predominant, or the unique tautomer, by

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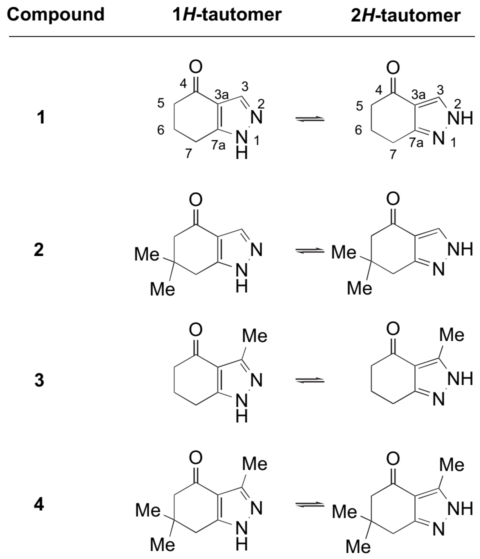


Figure 2. The four tetrahydroindazolones.

multinuclear NMR spectroscopy in solution and in solid state. Besides, in the cases of tetrahydroindazolones **2** and **4** the X-ray crystal structure was determined.

2. Results and discussion

2.1. Chemistry

4,5,6,7-Tetrahydroindazoles [3(5),4-tetramethylenepyrazoles] are usually prepared from cyclohexanone and its derivatives.[13,14] If instead of cyclohexanones, 1,3-cyclohexanediones are used, 1(2),5,6,7-tetrahydro-4*H*-indazol-4-ones are obtained.[15,16] These compounds (Fig. 3) have a rich reactivity with not less than four reactive positions that make them interesting scaffolds in medicinal chemistry.[17]

Known from a long time,[17–22] their chemistry was extensively studied by Sucrow et al. in 1970s and 1980s (see Ref. 24 for their reactivity)[23–29] with other significant contributions by Strakova and Gudriniece,[30] Akhrem (or Achrem),[31,32] Nunn and Rowell,[33] Schenone et al.,[34] Dalla Croce and La Rosa,[35] Le Tourneau and Peet,[36] Anderson-McKay et al.,[37] and Molteni et al.[38]

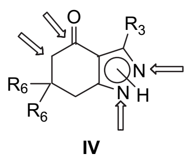
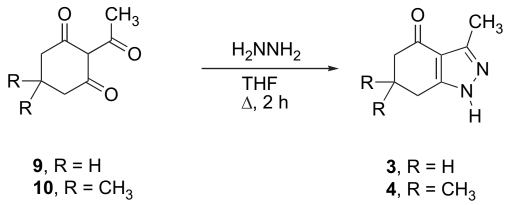


Figure 3. Reactivity of 6,6-disubstituted tetrahydroindazolones.

1(2),5,6,7-Tetrahydro-4*H*-indazol-4-one (**1**) and 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) (Scheme 1) were prepared according to the literature[38] starting from 1,3-cyclohexanedione (**5**) and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**6**), respectively, through the corresponding dimethylaminomethylene derivatives **7** and **8**.[34] Yields were moderate and their purification was achieved by column chromatography.

Similarly, 3-methyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**3**) and 3,6,6-trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) (Scheme 2) were synthesized[37] from 2-acetyl-1,3-cyclohexanedione (**9**) and 2-acetyldimedone (**10**) with satisfactory yields and their purification was straightforward (see Section 4).

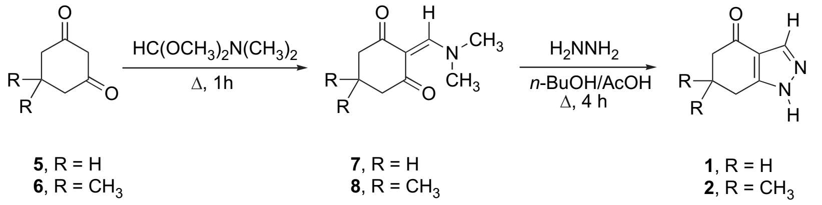


Scheme 2. Synthesis of compounds **3** and **4**.

Of the four compounds, only **2** was not previously reported. Since there are some discrepancies amongst the melting points (ours being measured by DSC) it is worth to recapitulate them here: compound **1** 163.8 °C (DSC), lit. 164–165 °C;[38] compound **2** 132.1 °C (DSC, new); compound **3** 160.3 °C (DSC), lit. 155 °C,[32] 152–154 °C;[35] compound **4** 101.4 °C (DSC), lit. 101–103 °C,[30] 101–102 °C,[31] 100.3–102.4 °C.[37]

2.2. Computational studies

On excluding OH-tautomers that are much less stable than the oxo forms,[39] the tautomerism of tetrahydroindazolones reduces, as in pyrazoles, to 1*H*- and 2*H*-tautomers. We already carried out computational studies (ab initio HF/6-31G*, HF/6-31G**, and DFT B3LYP/6-31G**)[39] establishing that in the gas phase tautomer 2*H* is the most stable one in all the four cases (B3LYP/6-31G**). On the other hand, according to HF/6-31G* and HF/6-31G** calculations, for derivatives **1** and **2**, tautomer 1*H* is more stable than 2*H* by about 0.65 kJ mol^{-1}, but for compounds **3** and **4** (with a methyl group at the 3-position) the 2*H* tautomer will be stabilized with respect to 1*H* by about 2 kJ mol^{-1}. The calculated dipole moments, by all methods, show that 1*H* tautomers have dipole moments nearly 2.5 times higher than 2*H* tautomers. Thus polar solvents will favor the 1*H* tautomer. In Table 1 we have summarized the results of



Scheme 1. Synthesis of compounds **1** and **2**.