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Regioselectivity in the formation of norbornene-fused pyrazoles: preparation of 1-substituted derivatives of 4,5,6,7-tetrahydro-1*H*-4,7-methanoindazole

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Abstract—The structural characteristics of (±)-(*exo*,*exo*)-3-(hydroxymethylene)-5,6-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one make the reactions between this β-diketone and hydrazines particularly interesting for elucidating the mechanism of pyrazole formation. The isolation and X-ray structure determination of two 5-hydroxy substituted Δ^2-pyrazolines [(±)-(3a*R**,4*R**,5*R**,6*S**,7*R**,7a*R**)-7a-hydroxy-5,6-(isopropylidenedioxy)-3a,4,5,6,7,7a-hexahydro-4,7-methano-1*H*-indazole] and [(±)-(3a*S**,4*R**,5*R**,6*S**,7*R**,7a*R**)-7a-hydroxy-5,6-(isopropylidene-dioxy)-1-phenyl-3a,4,5,6,7,7a-hexa-hydro-4,7-methano-1*H*-indazole] has been determinant for proposing a mechanism. Besides B3LYP/6-31G* calculations have been carried out on all intermediate dihydroxypyrazolidines and 5-hydroxypyrazolines. Finally, the annular tautomerism of the NH-methanotetrahydroindazoles has been studied both experimentally (^{13}C NMR) and theoretically: the Mills–Nixon effect favours the 2*H*-tautomer.
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1. Introduction

The reaction between a β-dicarbonyl compound and a hydrazine constitutes the main synthetic approach to the pyrazole ring.[1–5] The mechanism of this reaction has been studied several times,[6] we have represented in Scheme 1 a simplified plausible version. Recently, the **4**→**5** step has been studied in detail thanks to the isolation of several 5-hydroxypyrazolines **4**.[7] Note that when R^1=H, **5a** and **5b** become identical due to annular tautomerism, besides when R^1=H, **3a**=**3b**.

In this mechanism it is assumed that the dehydration steps, **3**→**4** and **4**→**5** are irreversible. An aspect that has not been clarified is the reversibility or not of the first step. It is possible that the reaction **1**+**2**→**3** is also irreversible and, consequently, the proportion of pyrazoles **5a** and **5b** will be determined by the structure of the dihydroxypyrazolidines **3a** and **3b**. But it is also possible that the dihydroxypyrazolidines **3a** and **3b** are in rapid equilibrium (through dissociation into **1**+**2**). If this is the case, then the rate-determining step will be the **3**→**4** transformation. Once pyrazolines **4** are formed, the final structure of pyrazoles **5** is decided.

Some of us have isolated and characterized a dihydroxypyrazolidine **3** [3,5-dihydroxy-3,5-bis(trifluoromethyl)-pyrazolidine],[8] as well as a series of 5-hydroxy-Δ^2-pyrazolines **3** stabilized by a CF_3 group at position 5 and/or by electron-withdrawing substituents at position N1 of the ring.[6] Other authors have characterized by ^{1}H NMR the intermediate dihydroxypyrazolidines **3** (with a spiro 4,4′-substituent).[9] It is therefore reasonable to assume the mechanism represented in Scheme 1.

In the general case of an asymmetrically substituted β-dicarbonyl compound ($R^2 \neq R^3$), the reaction can lead to a mixture of pyrazole isomers, **5a** and **5b** (Schemes 1 and 2). It is important to notice that the presence of two reactive centres in the hydrazine (**Z**, **Y**) and four more for the set of three tautomers of the dicarbonyl compound (**X**, **W**, **V**, **U**), results in eight different approximations for the reaction path (four for each final regioisomer).

In a preceding paper, we have described the synthesis and NMR structural determination of a series of pyrazoles fused to a bicyclo[2.2.1]heptane skeleton as synthetic

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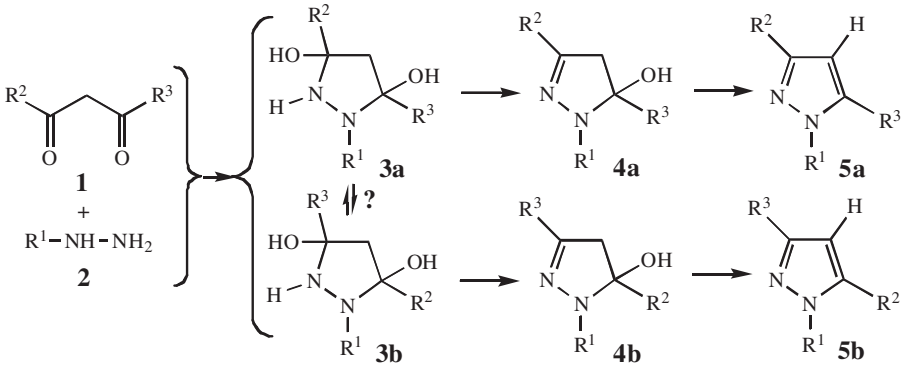
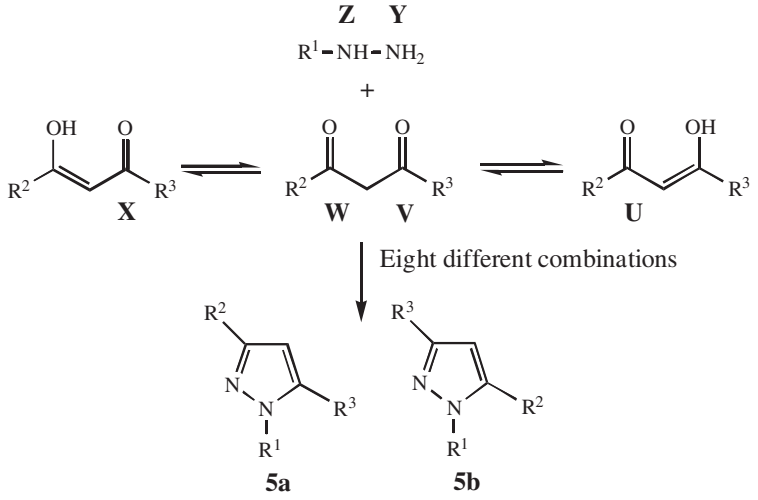


Scheme 1. The mechanism proposed for the synthesis of pyrazoles.



Scheme 2. The different ways to attain pyrazoles **5a** and **5b**.

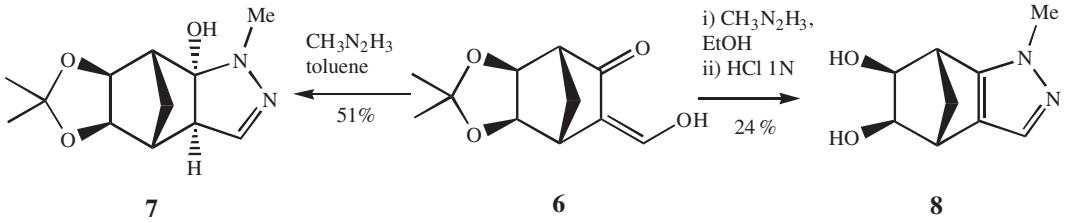
intermediates for the preparation of new azolo-condensed carbonucleosides.[10,11] The starting material was *exo*,*exo*-3-(hydroxymethylene)-5,6-(isopropylidenedioxy)bicyclo-[2.2.1]heptan-2-one (**6**), which reacted with several hydrazines to afford the corresponding pyrazoles. Amongst the interesting results is the fact that when **6** reacted with methylhydrazine during 3 h at room temperature in dry toluene, the only isolated compound (51% yield) was 5-hydroxy-Δ^2-pyrazoline **7** (Scheme 3). However, when, an acid catalysis was used (HCl aq in EtOH at reflux), in order to favor the formation of the pyrazole ring, the only isolated compound was **8** (24% yield). The easy isolation of **7** was a surprise since this structure lacks the two structural conditions we have previously reported (5-CF_3 and/or an EWG at position 1). We will discuss further on why the dehydration of **7** (Scheme 1, **4**→**5**) is difficult with the consequence that it can be isolated.

The total regioselectivity of this reaction (no N2-substituted derivatives were obtained) prompted us to study the reaction of **6** with other hydrazines and to gain a better understanding of the mechanism accounting for the results obtained.[12]

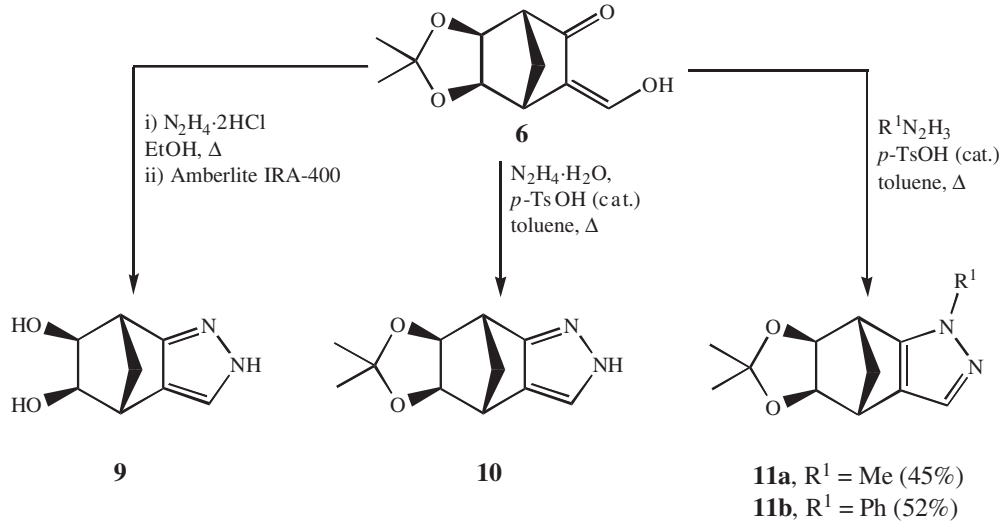
We will describe in the present work the study of the reactivity of hydroxymethyleneketone **6** with different hydrazines. We have isolated as many reaction intermediates as possible and studied their transformation into the corresponding pyrazole derivatives. Finally, a theoretical study will be reported describing our attempts to justify the observed regioselectivity.

2. Results and discussion

The first experiments were aimed to the direct preparation of pyrazoles from **6** and hydrazine dihydrochloride or



Scheme 3. Synthesis of pyrazoles **7** and **8** from the common precursor **6**.



Scheme 4. Preparation of pyrazoles **9**–**11**.

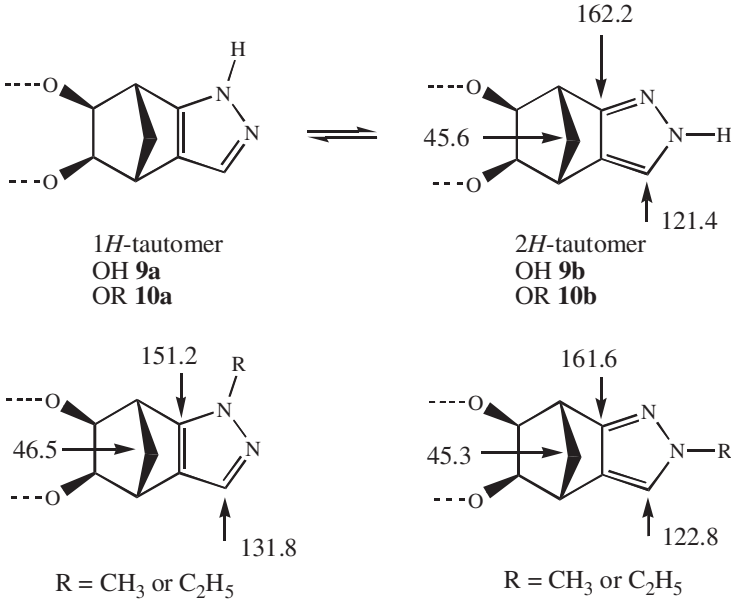
hydrazines in the presence of an acid catalyst to determine the synthetic accessibility of the resulting pyrazoles as well as the possible formation of isomer mixtures in the case of substituted hydrazines. Thus, NH-methanoindazoles **9** and **10** were obtained in acceptable yields (Scheme 4).[10,12]

The annular tautomerism of compounds **9** and **10** is interesting being related to the Mills–Nixon effect. We have been the first to extend the Mills–Nixon effect from its original definition concerning resonance forms[13] to the equilibrium present in tautomerism, first to pyrazoles[14–16] and then to enols of β-diketones.[17] These studies show that small rings favour the 2*H*-tautomers with an *endocyclic* single bond. A comparison of the ^{13}C chemical shifts of some selected C atoms (Scheme 5) leaves no doubt that these compounds are 2*H*-tautomers **b** as previously described.[10] Therefore, the bicyclo[2.2.1] ring system acts as a strained Mills–Nixon substituent.

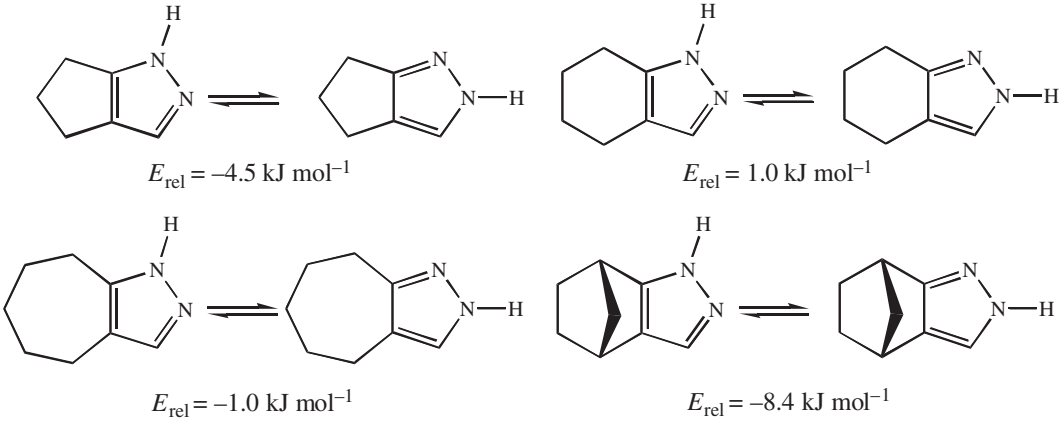
We have carried out computations (B3LYP/6-31G** together with frequency calculations) on four systems to assess the influence of the ring strain on the tautomerism of pyrazoles (Scheme 6).

It appears that the bicyclic system present in the compounds here described is much more efficient in directing the tautomerism towards 2*H*-pyrazoles than the five-membered ring. Compound **7** lacks both EWGs at positions 1 and 5, and so the reason of its stability must be different. We think it is related to the Mills–Nixon effect since pyrazole **11a** obtained from **7** has an endocyclic double bond, a situation clearly endergonic.

The reaction of the β-dicarbonyl compound **6** with methyl- and with phenylhydrazine in toluene at reflux and acid catalysis in a Dean–Stark apparatus afforded as sole reaction products the corresponding pyrazole derivatives substituted on N1, **11a** and **11b** (Scheme 4). A plausible explanation of



Scheme 5. The annular tautomerism of methanoindazoles **9** and **10**.



Scheme 6. Effect of ring strain on the annular tautomerism of polymethylenepyrazoles.

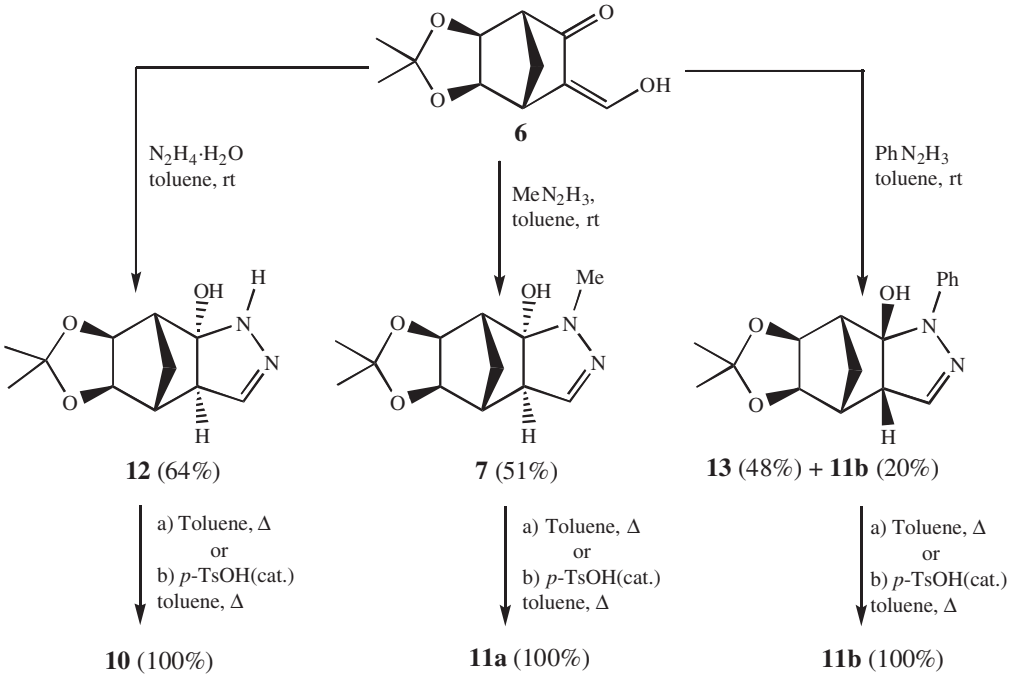
the observed regioselectivity is the existence of marked kinetic differences in the dehydration step of the proposed dihydroxypyrazolidines leading to the Δ^2-pyrazolines (Scheme 1, **2**→**3**).

To establish that the steps following the formation of the hydroxypyrazolines do not affect the final outcome and taking advantage of the stability of 1-methyl-5-hydroxypyrazoline **7** (Scheme 3),[10] we decided to isolate and characterize the remaining hydroxypyrazolines as well as to study their transformation into the corresponding pyrazoles (Scheme 7).

The experiments we decided to carry out were: (i) to use the experimental conditions that allow isolating the intermediate **7** from **6**,[10] (ii) to determine the structure of the isolated compounds (in particular the possible existence of regio- and/or stereoisomers) and (iii) the study of the conversion of the hydroxypyrazolines into pyrazoles with and without acid catalysis.

From the experiments we carried out, it is worth to note the formation of the hydroxypyrazolines **7**, **12** and **13** that were isolated in acceptable yields (Scheme 7). The hydroxypyrazolines **12**, **7** and **13** were quantitatively transformed into the corresponding pyrazoles **10**, **11a** and **11b**, independently of the use or not of acid catalysis, only changing the reaction times (Table 1).

In the reaction with phenylhydrazine although the conditions were those to obtain **13**, a significant amount (20%) of pyrazole **11b** was isolated. We will turn now to the reason why the *N*-phenylpyrazoline **13** dehydrates more easily than the *N*-H **12** and *N*-methyl **7** pyrazolines. As we discussed before, an EWG R^1 at position 1 (**4**) stabilizes the hydroxypyrazoline; it is true that the electronic properties of the phenyl group are not so marked as those of typical stabilizing groups such as $CONH_2$ (σ_p=0.38), SO_2R (σ_p=0.73) that allow to isolate **4**,[6] but nevertheless, the phenyl group (σ_p=0.01) is more EWG than the methyl (σ_p=−0.17).[18] The additional conjugation between the



Scheme 7. The 5-hydroxy-Δ^2-pyrazolines and their conversion into pyrazoles.

Table 1. Conditions to transform hydroxypyrazolines **12**, **7** and **13** into the corresponding pyrazoles **10**, **11a** and **11b**

Process	Catalysis	Time (h)	Conversion (%)
12→10	None	48	100
12→10	TsOH	0.25	100
7→11a	None	60	100
7→11a	TsOH	0.25	100
13→11b	None	48	100
13→11b	TsOH	0.25	100

phenyl group and the pyrazole ring in **5** (**11b** in Scheme 7) could be the driving force that facilitates the dehydration in the case of pyrazoline **13** compared with **7** and **12**.

The structural assignment and the stereochemistry of the hydroxypyrazolines **12** and **13** was determined by X-ray diffraction on single crystals of these two compounds (Figs. 1 and 2).

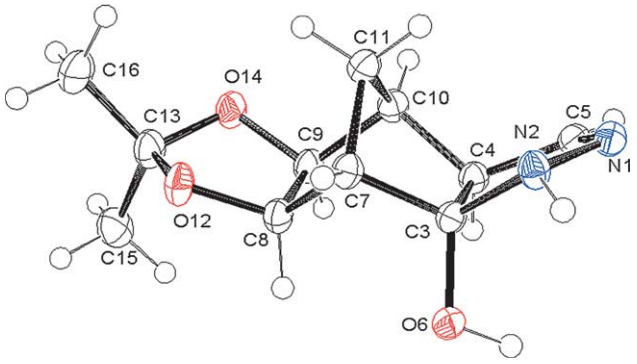


Figure 1. ORTEP projection of the molecular structures of compound **12**.

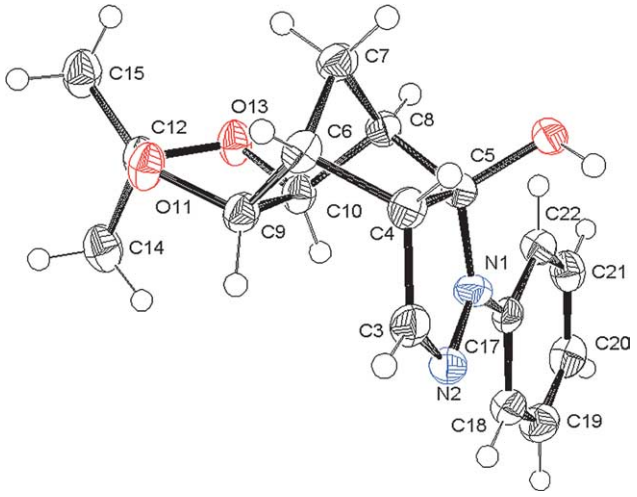


Figure 2. ORTEP projection of the molecular structures of compound **13**.

We have represented in Scheme 8 a more detailed mechanism than that depicted in Scheme 1 in what concerns the intermediate steps of the 3,5-dihydroxypyrazolidines and hydroxypyrazolines only for $R^1=H$ (**1** series) and $R^1=CH_3$ (**2** series) and $R^1=C_6H_5$ (**3** series). We have included tentatively equilibrium arrows between the pyrazolidines. When $R^1=H$, **A1**=**C1**, **B1**=**D1**, **E1**=**G1** and **F1**=**H1**. Remember that the two hydroxypyrazolines that have been isolated and their X-ray structure determined correspond to the following molecules in Scheme 8: **12** and **13** are, respectively, **K1** and **N3**.

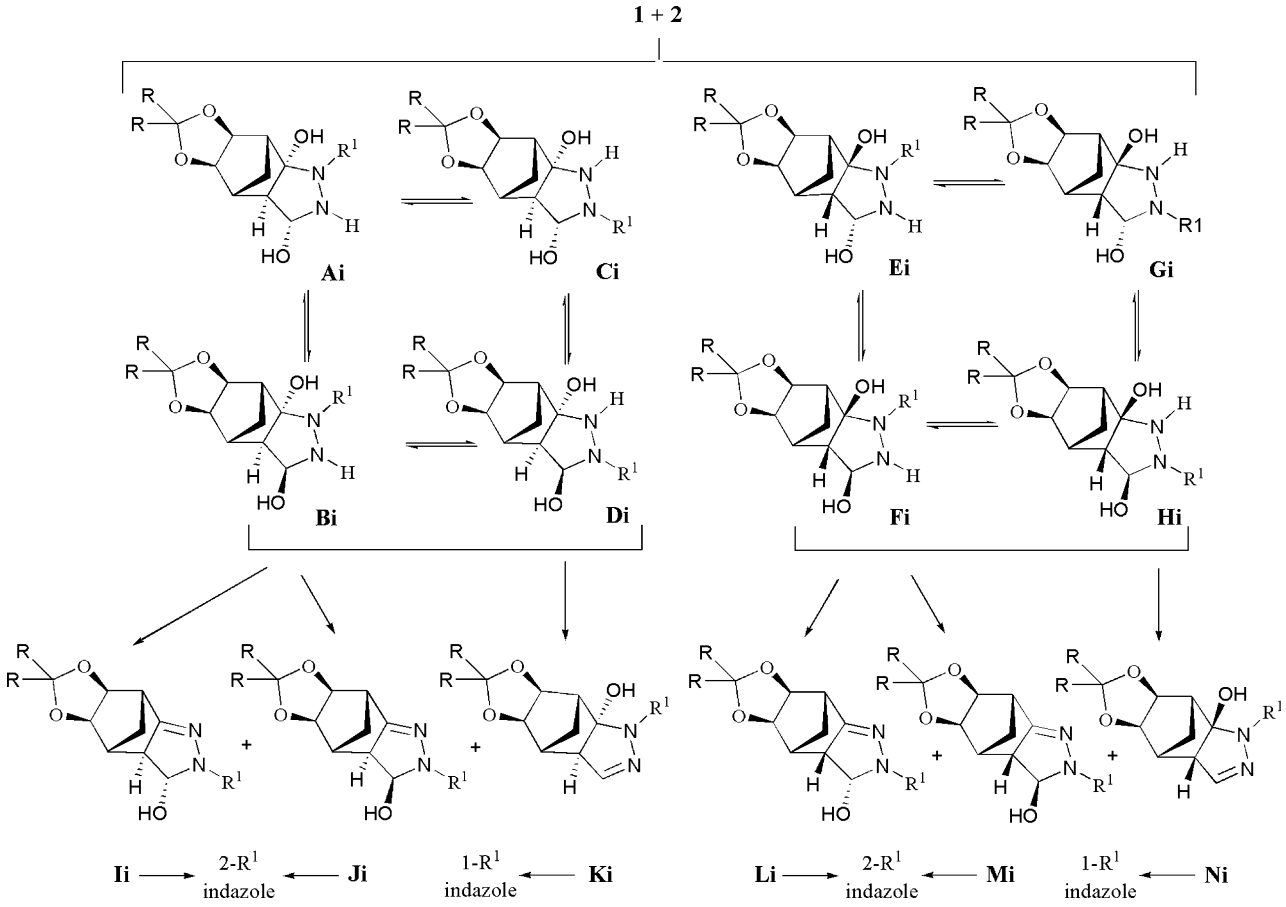
We carried out B3LYP/6-31G* calculations of the compounds of Scheme 8 belonging to the series **1** and **2**: four NH pyrazolidines, six NH pyrazolines, eight *N*-methyl pyrazolidines and six *N*-methylpyrazolines with the only simplification of replacing the methyl groups R of the 1,3-dioxolane ring by protons. The results are reported in Table 2. Although it is probable that the ordering of relative energies calculated for the *N*-methyl series **2** should be approximately valid for the *N*-phenyl series **3**, some discrepancies could be related to a specific effect of the phenyl ring.

Table 2 deserves some comments.

(1) The most stable hydroxypyrazolines have the structure **Ki**. Structure **K1** corresponds to compound **12** but the isolated *N*-phenyl derivative has the structure **N3**, which, in the *N*-methyl series is **N2** that lies only 10.6 kJ mol^{-1} above the minimum **K2**.
(2) The most stable dihydroxypyrazolidines have the structures **A1** (or **C1**) followed by **B1** (or **D1**) in the NH series **1** while in the *N*-methyl series the stability order is **D2**>**C2**>**A2**>**B2**.
(3) The final pyrazoles having the structures **11a** and **11b** must be formed by dehydration of **Ki** or **Ni**. The NH derivative **10** cannot be used for this discussion because all the ways led to tautomer 2*H*.
(4) The synthetic sequences could be: NH-series, **A1**→**K1**→**10**; *N*-methyl series, **D2**→**K2**→**11a**; *N*-phenyl series, **H3**→**N3**→**11b**. It is not necessary to assume an equilibration of the pyrazolidines.
(5) This analysis assumes that the process from the initial substrates (the hydroxymethyleneketone **6** and the corresponding hydrazine) to the different hydroxypyrazolines must be endergonic. Thus, even if this is a kinetic controlled process, the Hammond principle should apply, that is, the transition states should be product-like and their relative stabilities must be proportional to the relative stabilities of the products that will be formed.

3. Conclusions

Reactions of substituted hydrazines with appropriate derivatives of bicyclo[2.2.1]heptane preferably lead to the formation of 1-substituted derivatives of 4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole. This regioselectivity can be explained taking into account a plausible mechanism for the formation of pyrazoles from 1,3-dicarbonyl compounds, the structures of the isolated intermediate hydroxypyrazolines and the theoretical calculations of the stability of the intermediate dihydroxypyrazolidines and hydroxypyrazolines. Angular tension due to the carbocyclic system fused to the heterocyclic moiety seems to be a stabilizing factor of the hydroxypyrazolines structures as efficient as an EWG in the case of acyclic precursors.



R^1 = H, series **1**, R^1 = Me, series **2**, R^1 = Ph, series **3** ($\mathbf{A_1}$ to $\mathbf{N_3}$). Experimental R = CH_3, calculated R = H

Scheme 8. Dihydroxypyrazolidine and hydroxypyrazoline intermediates.

Table 2. Relative values of the energy (kJ mol^{-1}) of the molecules of Scheme 8

Compound	Series **1** (*N*-H)	E_{rel}	Series **2** (*N*-CH_3)	E_{rel}
Ai	**A1**	**0.00**	**A2**	7.72
Bi	**B1**	5.12	**B2**	10.08
Ci	**C1**	[0.00]	**C2**	3.26
Di	**D1**	[5.12]	**D2**	**0.00**
Ei	**E1**	23.18	**E2**	31.86
Fi	**F1**	13.04	**F2**	18.23
Gi	**G1**	[23.18]	**G2**	16.91
Hi	**H1**	[13.04]	**H2**	13.38
Ii	**I1**	44.96	**I2**	40.01
Ji	**J1**	40.20	**J2**	40.44
Ki	**K1**	**0.00**	**K2**	**0.00**
Li	**L1**	43.28	**L2**	43.08
Mi	**M1**	45.59	**M2**	40.21
Ni	**N1**	9.93	**N2**	10.61

4. Experimental

4.1. General

All chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. and used without further purification. Hydroxymethyleneketone **6** was freshly prepared before its use.[19] Melting points were measured in a Reichert Kofler Thermopan and are uncorrected. Infrared spectra were recorded in a Perkin-Elmer 1640 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in a Bruker AMX 300 spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts in δ values, J in Hz). Mass spectra were recorded on a Kratos MS-59 spectrometer. Microanalyses were performed in a Perkin-Elmer 240B Elemental Analyser at the University of Santiago Microanalysis Service. Analyses indicated by the symbols of elements were within $\pm$0.4% of the theoretical values. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TCL on pre-coated silica gel plates (Merck 60 F_{254}, 0.25 mm). X-ray diffraction data were collected in an Enraf-Nonius CAD4 automatic diffractometer using the program CAD4-EXPRESS.[20]

4.1.1. ($\pm$)-(3a*R,4*R**,5*R**,6*S**,7*R**,7a*R**)-7a-Hydroxy-5,6-(isopropylidenedioxy)-3a,4,5,6,7,7a-hexahydro-4,7-methano-1*H*-indazole (12).** Hydrazine monohydrate (0.28 mL, 9.04 mmol) was added under argon to a well-stirred solution of freshly prepared **6** (0.95 g, 4.52 mmol) in dry toluene (25 mL), and the mixture was stirred for 3 h at room temperature. By simple filtration of the reaction mixture compound **12** was isolated (0.65 g; 64%). Compound **12** is a lightly coloured solid that was crystallized from EtOAc; mp 192–195 °C. IR (KBr) ν (cm^{-1}): 3314, 3098, 2994, 2973, 2950, 2910, 2860, 1594, 1460,

1406, 1380, 1304, 1272, 1206, 1180, 1165, 1122, 1068, 1047, 866, 846, 653. ^{1}H NMR ($CDCl_3$) δ (ppm): 6.64 (s, 1H, 3-H); 5.80 (br s, 1H, D_2O exchange, NH); 4.68 (d, 1H, J=5.4 Hz, 6-H); 4.30 (d, 1H, J=5.1 Hz, 5-H); 2.47 (virtual s, 1H, D_2O exchange, OH); 2.42–2.39 (m, 3H); 1.70 (dd, 1H, J=11.3, 1.6 Hz, 8-H*H*); 1.45 (s, 3H, CH_3); 1.32 (s, 3H, CH_3); 1.25 (dd, 1H, J=11.3, 1.3 Hz, 8-*H*H). ^{13}C NMR and DEPT ($CDCl_3$) δ (ppm): 124.90 (C), 121.56 (CH), 114.89 (C), 83.24 (CH), 82.18 (CH), 45.93 (CH_2), 42.88 (CH), 41.72 (CH), 26.29 (CH_3), 24.67 (CH_3). EIMS *m*/*z* (%): 224 (M, 4), 209 (19), 149 (41), 119 (21), 97 (26), 85 (100), 84 (23), 83 (27), 82 (52), 81 (18), 77 (15), 66 (15), 65 (16), 59 (16), 55 (30), 53 (18). Single crystals suitable for X-ray diffractometry were obtained by dissolving crystals of **12** in the minimum quantity of cold ether in an open vial that was then placed in a larger container with a little pentane in its bottom; the container was closed, and after a few days in a cool, dark place free from vibrations afforded the desired single crystals.

4.1.2. (±)-(3a*S,4*R**,5*R**,6*S**,7*R**,7a*R**)-7a-Hydroxy-5,6-(isopropylidenedioxy)-1-phenyl-3a,4,5,6,7,7a-hexahydro-4,7-methano-1*H*-indazole (13) and (±)-(*exo*,*exo*)-5,6-(isopropylidenedioxy)-1-phenyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (11b).** Phenylhydrazine (1.7 mL, 8.66 mmol) was added under argon to a well-stirred solution of freshly prepared **6** (0.91 g, 4.33 mmol) in dry toluene (25 mL) and the mixture was stirred for 5 h at room temperature, after which removal of the solvent under reduced pressure left a reddish solid residue (2.56 g) that was purified by column chromatography over silica gel using as eluent mixtures of hexane/EtOAc of different ratios 15/1, 10/1 and 5/1. From the fractions of the second eluent mixture (10/1) was obtained **11b** after removing the solvent under reduced pressure (0.25 g, 20%). Similarly, from the fractions corresponding to the third eluent (5/1) was obtained **13** (0.62 g, 48%) as a reddish residue that mixed with pentane and filtered afford a slightly coloured solid. Compound **11b**. White solid that was crystallized from pentane; mp=102–103 °C. IR (KBr) ν (cm^{-1}): 3006, 2982, 2952, 2920, 1600, 1511, 1486, 1454, 1427, 1378, 1205, 1165, 1024, 998, 982, 902, 867, 787, 759, 692, 639. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.62 (d, 2H, J=7.9 Hz, 2′H+6′H); 7.43 (t, 2H, J=7.7 Hz, 3′H+5′H); 7.38 (s, 1H, 3-H); 7.28–7.27 (m, 1H, 4′-H); 4.32 (dd, 2H, J=16.3, 4.7 Hz, 5-H+6-H); 3.61 (virtual s, 1H, 7-H); 3.28 (virtual s, 1H, 4-H); 2.56 (d, 1H, J=9.2 Hz, 8-*H*H); 2.35 (d, 1H, J=9.2 Hz, 8-H*H*); 1.53 (s, 3H, CH_3); 1.31 (s, 3H, CH_3). ^{13}C NMR and DEPT ($CDCl_3$) δ (ppm): 149.97 (C), 139.87 (C), 133.92 (CH), 133.89 (CH), 129.79 (C), 129.43 (CH), 126.45 (CH), 119.55 (CH), 114.45 (C), 82.88 (CH), 81.06 (CH), 46.57 (CH_2), 44.76 (CH), 41.82 (CH), 26.03 (CH_3), 24.39 (CH_3). EIMS *m*/*z* (%): 283 (M+1, 2), 282 (M, 5), 196 (16), 195 (100), 183 (10), 182 (61), 181 (16), 168 (14), 167 (21), 154 (12), 128 (7), 115 (6), 92 (10), 85 (18), 77 (88), 63 (13), 59 (22), 52 (16), 51 (70). Compound **13**. Yellowish solid that was crystallized from Et_2O/hexane; mp=180–185 °C. IR (KBr) ν (cm^{-1}): 3382, 2990, 2972, 2942, 1601, 1503, 1382, 1363, 1272, 1263, 1242, 1208, 1159, 1118, 1083, 1063, 1048, 1036, 971, 900, 870, 860, 792, 743. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.32–7.28 (m, 4H); 6.94–6.89 (m, 1H, 4′-H); 6.69 (d, 1H, J=1.6 Hz, 3-H); 4.01 (d, 1H, J=4.7 Hz, 6-H); 3.89 (d, 1H, J=5.4 Hz, 5-H); 3.28 (d, 1H, J=4.8 Hz, 3a-H); 3.01 (virtual s, 1H, 7-H); 2.68 (d, 1H, J=5.1 Hz, 4-H); 2.52 (s, 1H, D_2O exchange, OH); 2.04 (d, 1H, J=10.8 Hz, 8-*H*H); 1.89 (dd, 1H, J=9.3, 1.4 Hz, 8-H*H*); 1.41 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). FABMS: *m*/*z* (%): 300.12 (M, 8), 283.12 (M−OH, 100). Single crystals suitable for X-ray diffractometry were obtained by dissolving crystals of **13** in the minimum quantity of cold ether in an open vial that was then placed in a larger container with a little hexane or cyclohexane in its bottom; the container was closed, and after a few days in a cool, dark place free from vibrations afforded the desired single crystals.

4.2. Preparation of methanoindazoles by reaction de (±)-(*exo*,*exo*)-3-(hydroxymethylene)-5,6-(isopropylidendioxi)-bicyclo[2.2.1]heptan-2-one (6) with hydrazine and mono-substituted hydrazines. General method

To a rapidly-stirred solution of **6** (1 mmol) in freshly prepared dry toluene under Ar atmosphere and at room temperature was added in a single addition the corresponding hydrazine (1.2 mmol) and a catalytic amount of TsOH. The reaction mixture was refluxed in a Dean–Stark apparatus for 12 h. Once eliminated the solvents under reduced pressure, the remaining residue was purified by column chromatography over silica gel.

4.2.1. (±)-(*exo*,*exo*)-5,6-(Isopropylidenedioxy)-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (10). Eluent, hexane/EtOAc 1:1. Yield 67%. White solid with mp and spectroscopic features identical to those previously described.[10]

4.2.2. (±)-(*exo*,*exo*)-5,6-(Isopropylidenedioxy)-1-methyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (11a). Eluent, hexane/EtOAc 1:1. Yield 45%. Dense colourless oil with spectroscopic features identical to those previously described.[10]

4.2.3. (±)-(*exo*,*exo*)-5,6-(Isopropylidenedioxy)-1-phenyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (11b). Eluent, hexane/EtOAc 15:1. Yield 52%. The spectroscopic data are identical to those above reported for the compound **11b**.

4.3. Transformation of pyrazolines into pyrazoles. General method

The corresponding pyrazoline (**12**, **7** or **13**; 0.21 mmol) dissolved in dry toluene (15 mL) was heated at reflux in a Dean–Stark apparatus during the time indicated in Table 1. When the reaction is completed (followed by TLC), the solvent was eliminated under reduced pressure and the resulting pyrazoles (**10**, **11a** and **11b**) were identified by their spectroscopic data. In the case of reactions carried out under acid catalysis, to the initial toluene solution was added a small amount of TsOH (3–5 mg) resulting in a much shorter reaction time (Table 1).

4.4. Computational details

B3LYP/6-31G* calculations with complete optimization of the geometry (maxima have been checked with frequency calculations) have been carried out.[21,22] In the case of the annular tautomerism (Scheme 6) the absolute values of

the energy of the most stable tautomer are: trimethylenepyrazole (2*H*: −342.94089 hartree); tetramethylenepyrazole (1*H*: −382.27423 hartree); pentamethylenepyrazole (2*H*: −421.59084 hartree); bicyclic derivative (2*H*: −420.34352 hartree). Particular care is necessary to obtain the minimum energy conformations of the seven membered rings, the pseudo-chair form.[23]

In the case of the pyrazolidines and pyrazolines of Scheme 8, we have calculated two conformations of the OH group (compounds **Li**, **Mi** and **Ni**) that with the OH pointing towards the interior of the ring being the most stable. The energies of the absolute minima are: **A1**=**C1** (R^1=H, −761.69862 hartree), **K1** (R^1=H, −685.27996 hartree), **D2** (R^1=CH_3, −761.69862 hartree), **K2** (R^1=CH_3, −724.59130 hartree).

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