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SYNTHESIS, ^{1}H AND ^{13}C NMR STUDY OF PYRAZOLES DERIVED FROM CHIRAL CYCLOHEXANONES (3-METHYLCYCLOHEXANONE, MENTHONE, PULEGONE, DIHYDROCARVONE AND CARVONE)

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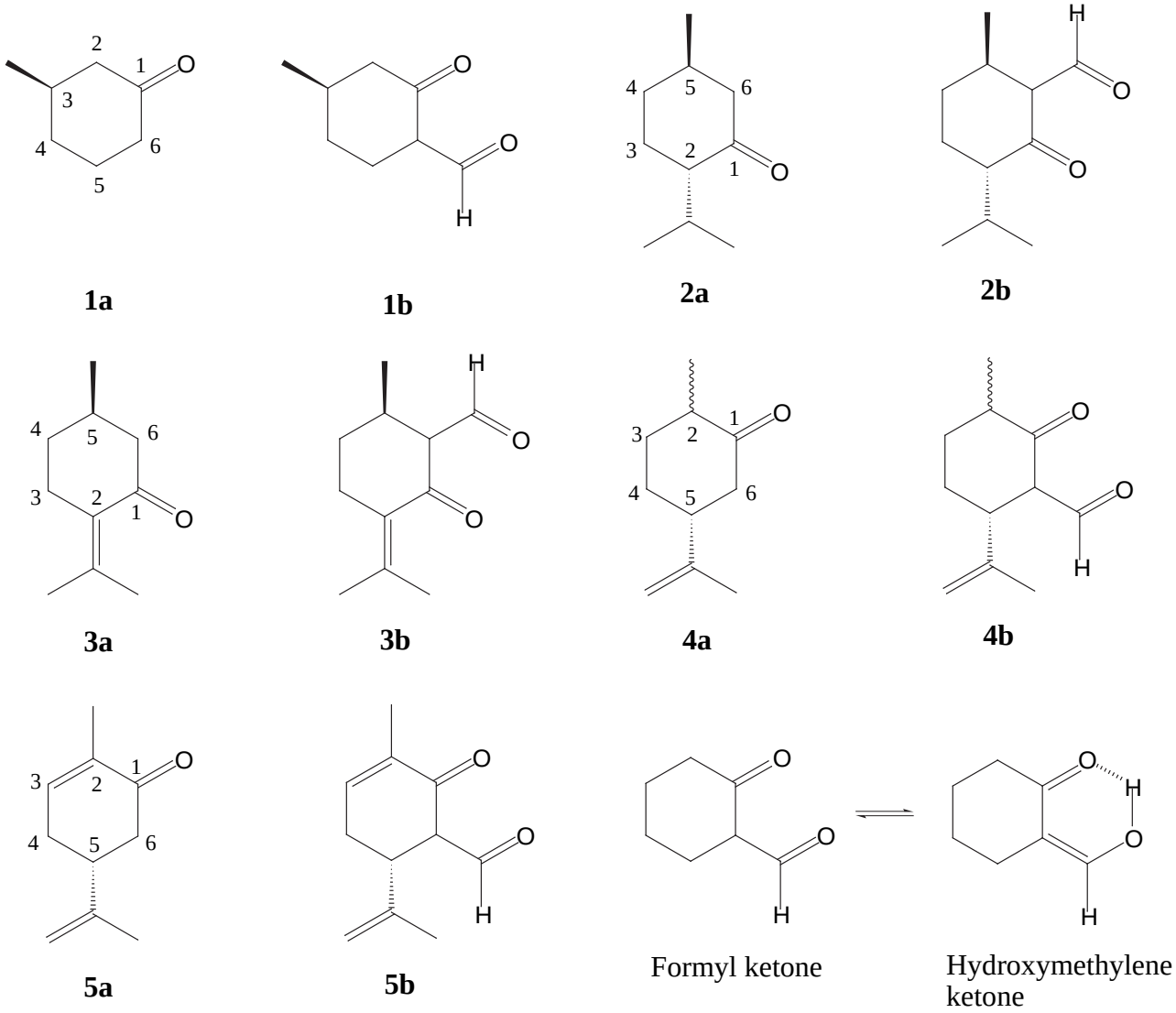
Abstract– The ^{1}H and ^{13}C chemical shifts of four tetrahydroindazoles (two of them existing as diastereomeric mixtures) and one aldazine were measured and assigned. These compounds were obtained from monoterpenic ketones (*R*)-(+)-3-methylcyclohexanone, (*2S,5R*)-(-)-menthone, (*R*)-(+)-pulegone, (*5R*)-(+)-dihydrocarvone, and (*R*)-(-)-carvone in a two-step procedure. The annular tautomerism in $CDCl_3$ solution was calculated and compared with *ab initio* calculations (B3LYP/6-31G*).

INTRODUCTION

As a consequence of the increased use of pyrazole ligands in coordination chemistry including catalytic applications, the synthesis and characterisation of chiral pyrazoles have become a subject of interest. Several years ago, some of us prepared pyrazoles from natural products in search of olfactory properties. The starting ketones were (+)-methyl-3-cyclohexanone,[1] menthone,[2] isopinocamphone,[3] camphor[4] and (+)-pulegone.[5] Due to patent difficulties, the work carried out before 1973[6] was published only in 1988,[1-5] consequently, the spectroscopic identification was mostly based on ^{1}H NMR at 60 MHz. Other publications dealing with the synthesis and characterisation of pyrazoles derived from naturally occurring cyclic chiral compounds (or they derivatives) are related to camphor,[7-13] pulegone,[12,14] *p*-menthane,[15] bornane,[16] α-pinene,[17] menthone,[10,15,18] 3-carene[19] and isopropylidenenorbornene.[20]

The present paper reports the products obtained from cyclic ketones having a methylene group α to the carbonyl: (*R*)-(+)-3-methylcyclohexanone (**1a**), (*2S,5R*)-(-)-menthone (**2a**), (*R*)-(+)-pulegone (**3a**), (*5R*)-(+)-dihydrocarvone (**4a**), and (*R*)-(-)-carvone (**5a**) (Scheme 1). Compound (**4a**) is sold (Aldrich 21,828-6) as a mixture of *2R* and *2S* isomers.

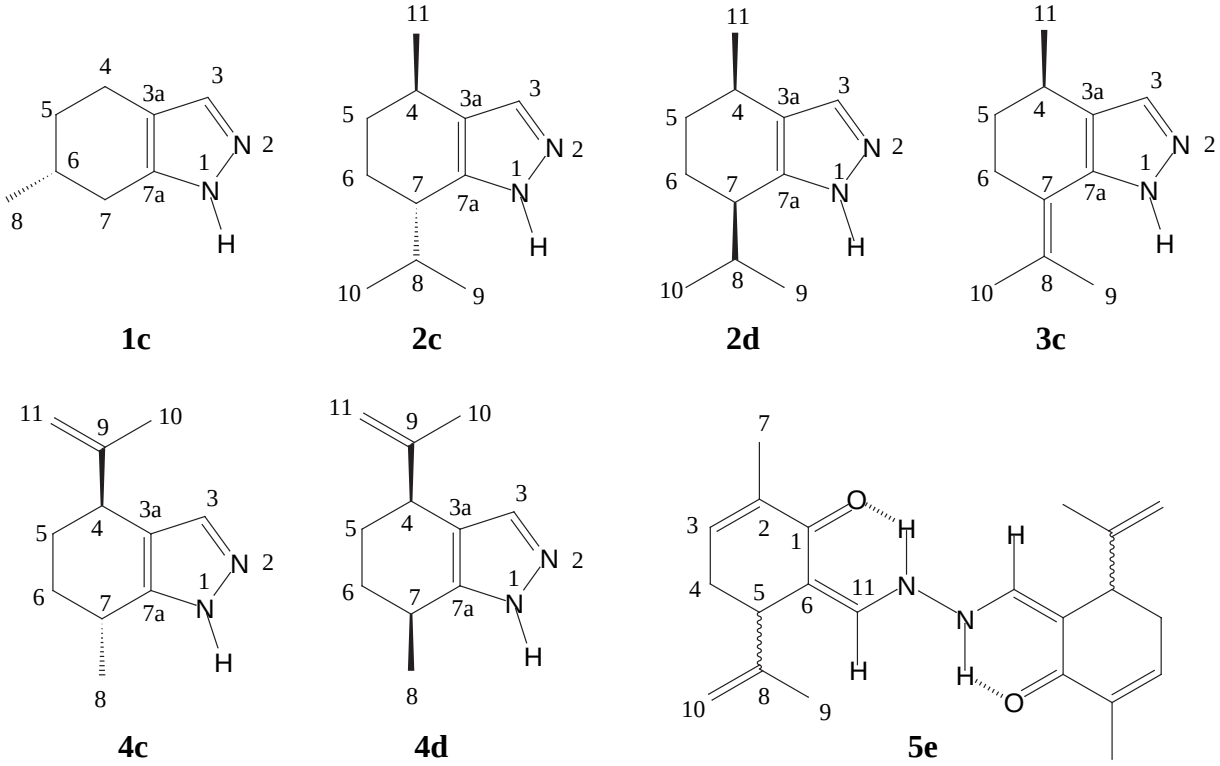


Scheme 1

RESULTS AND DISCUSSION

Chemistry. The five ketones (**1a-5a**) are commercial products. The formylation was carried out by ethyl formate on the corresponding enolates: the β-diketones were obtained with the following yields, **1b** (89%), **2b** (45%), **3b** (55%), **4b** (61%), and **5b** (64%). These compounds, relatively unstable and air-sensitive have not been studied by NMR spectroscopy nor their tautomerism determined. The second step

consists in the reaction of the β-diketones with hydrazine hydrate in methanol. The following pyrazole (tetrahydroindazoles) were obtained: (6*R*)-6-methyl-4,5,6,7-tetrahydro-1(2)*H*-indazole (**1c**), a mixture of (4*R*,7*S*)-4-methyl-7-(isopropyl)-4,5,6,7-tetrahydro-1(2)*H*-indazole (**2c**, major) and (4*R*,7*R*)-4-methyl-7-isopropyl-4,5,6,7-tetrahydro-1(2)*H*-indazole (**2d**, minor), (4*R*)-4-methyl-7-(1-methylethylidene)-4,5,6,7-tetrahydro-1(2)*H*-indazole (**3c**), a mixture of (4*S*,7*R*)-4-isopropylidene-7-methyl-4,5,6,7-tetrahydro-1(2)*H*-indazole (**4c**, major) and (4*S*,7*S*)-4-isopropylidene-7-methyl-4,5,6,7-tetrahydro-1(2)*H*-indazole (**4d**, minor), hydroxymethylenearvone azine (**5e**) (Scheme 2).



Scheme 2

The two mixtures of diastereoisomers, compounds (**2**) and (**4**), have different origins. In the case of **2**, the epimerization probably occurs on the β-keto aldehyde (**2b**) and involves the C-2 center, while in the case of **4** it is a consequence of **4a** being a mixture of enantiomers.

NMR ($CDCl_3$) spectroscopy. ^{1}H NMR signals were completely and unambiguously assigned on the basis of the proton-proton connectivity network established from the COSY spectra. The ^{13}C NMR assignment of the protonated carbons followed from the analysis of one-bond heteronuclear correlation data (HMQC spectra). Finally, the quaternary carbons were unequivocally determined from the long-range correlation responses observed with the previously assigned ^{1}H signals in the HMBC diagrams.

For pyrazoles (**2**) and (**4**) (both studied as mixtures), some ^{1}H signals present strong overlaps precluding the accurate measurement of chemical shifts and coupling constants for these signals. However, this latter information was indirectly available from the 1D-HOHAHA experiments in which the semi-selective excitation of selected protons (CH_3) was achieved with Gaussian-shaped (gs) pulses. The results for tetrahydroindazoles (**1**-**4**) are collected in Tables 1 (^{1}H NMR) and 2 (^{13}C NMR).

Table 1. ^{1}H chemical shifts (ppm) and ^{1}H-^{1}H coupling constants (Hz) of tetrahydroindazoles (**1**-**4**)

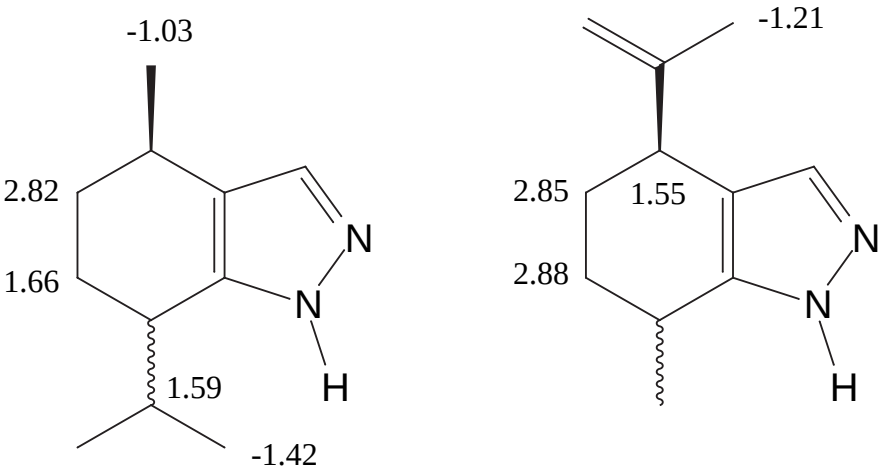
1c: 1.08 (3H, d, *J* = 6.6, H-8), 1.39 (1H, dtd, *J* = 16.0, 10.5, 5.5, H-5β), 1.92 (2H, m, H-5α and H-6α), 2.37 (1H, dd, *J* = 17.3, 10.1, H-7β), 2.50 (1H, ddd, *J* = 16.0, 10.5, 5.5, H-4a), 2.66 (1H, ddd, *J* = 16.0, 5.1, 3.6, H-4β), 3.04 (1H, dd, *J* = 17.3, 5.2, H-7α), 7.74 (1H, s, H-3).
2c: 0.72 (3H, d, *J* = 6.8, H-9), 1.03 (3H, d, *J* = 6.8, H-10), 1.20 (3H, d, *J* = 6.8, H-11), 1.50 (1H, m, H-6), 1.78 (1H, m, H-5), 1.95 (1H, m, H-6), 2.01 (1H, m, H-5), 2.65 (1H, qd, *J* = 6.8, 4.4, H-4), 2.71 (1H, hept, d, *J* = 6.8, 4.0, H-8), 2.88 (1H, dddd, *J* = 11.1, 5.4, 4.0, 1.0, H-7), 7.62 (1H, d, *J* = 1.0, H-3).
2d: 0.81 (3H, d, *J* = 6.8, H-9), 1.06 (3H, d, *J* = 6.8, H-10), 1.18 (3H, d, J = 6.5, H-11), 1.55 (1H, m, H-5), 1.75 (1H, m, H-6), 1.80 (2H, m, H-5 and H-6), 2.46 (1H, hept, d, *J* = 6.8, 5.6, H-8), 2.81 (1H, qdd, *J* = 6.8, 5.6, 4.0, H-4), 2.81 (1H, q, *J* = 6.5, H-7), 7.61 (1H, br s, H-3).
3c: 1.21 (3H, d, *J* = 6.8, H-11), 1.32 (1H, dddd, *J* = 13.0, 12.0, 9.6, 3.6, H-5β), 1.85 (3H, br s, H-9), 1.92 (1H, dtd, *J* = 13.0, 5.3, 3.7, H-5α), 2.11 (3H, br s, H-10), 2.21 (1H, ddm, *J* = 14.9, 12.0, H-6α), 2.65 (1H, dt, *J* = 14.9, 4.6, H-6β), 2.74 (1H, dqd, *J* = 9.6, 6.8, 4.6, H-4α), 7.37 (1H, s, H-3).
4c: 1.44 (3H, d, *J* = 7.0, H-8), 1.60 (1H, m, H-5), 1.71 (3H, br s, H-10), 1.75-1.90 (3H, m, H-5 and H-6), 3.07 (1H, hex, *J* = 7.0, H-7), 3.34 (1H, t, *J* = 6.2, H-4), 4.52 (1H, br s, H-11), 4.88 (1H, br s, H-11), 7.52 (1H, br s, H-3).
4d: 1.49 (3H, d, *J* = 6.8, H-8), 1.62 (3H, br s, H-10), 1.75-1.90 (2H, m, H-5), 1.98 (1H, m, H-6), 2.10 (1H, m, H-6), 2.98 (1H, dq, *J* = 9.0, 6.8, H-7), 3.34 (1H, t, *J* = 6.2, H-4), 4.79 (1H, br s, H-11), 4.87 (1H, br s, H-11), 7.51 (1H, br s, H-3).

Table 2. ^{13}C chemical shifts (ppm) of tetrahydroindazoles (**1**-**4**)

1c: 21.21 (C-4), 23.16 (C-8), 30.57 (C-6), 30.71 (C-5), 32.59 (C-7), 119.14 (C-3a), 131.19 (C-3), 146.79 (C-7a).
2c: 16.60 (C-9), 20.30 (C-10), 20.84 (C-11), 21.37 (C-6), 27.20 (C-8), 29.68 (C-4), 31.70 (C-5), 38.79 (C-7), 124.39 (C-3a), 128.96 (C-3), 147.06 (C-7a).

2d: 18.02 (C-9), 19.71 (C-6), 20.87 (C-10), 21.87 (C-11), 25.61 (C-8), 28.88 (C-5), 30.47 (C-4), 37.99 (C-7), 123.77 (C-3a), 129.20 (C-3), 146.89 (C-7a).
3c: 21.28 (C-11), 22.04 (C-9), 22.79 (C-10), 27.60 (C-4), 27.64 (C-6), 33.16 (C-5), 121.27 (C-7), 123.17 (C-3a), 126.61 (C-8), 133.05 (br, C-3), 142.05 (br, C-7a).
4c: 20.27 (C-8), 20.40 (C-10), 25.12 (C-5), 26.92 (C-7), 27.79 (C-6), 39.06 (C-4), 113.62 (C-11), 119.25 (C-3a), 130.11 (C-3), 146.22 (C-7a), 149.26 (C-9).
4d: 19.19 (C-10), 19.70 (C-8), 27.97 (C-5), 28.07 (C-7), 30.67 (C-6), 40.61 (C-4), 113.47 (C-11), 119.77 (C-3a), 130.01 (C-3), 145.67 (C-7a), 149.05 (C-9).

Conformation. We have summarized in Scheme 3 the most significant differences of $\delta^{13}C$ chemical shifts (> 1 ppm) between pairs of diastereoisomers (*trans–cis*).

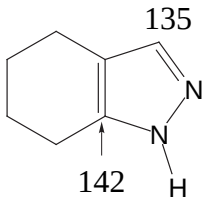


2c–2d **4d–4c**

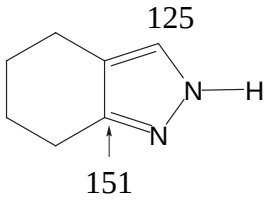
Scheme 3

Tautomerism. For each of these tetramethylenepyrazoles (tetrahydroindazoles) two annular tautomers are possible: the 1*H* (represented) and the 2*H*. It has been established, using ^{13}C and ^{15}N NMR spectroscopies, that a compound related to **1c** (with a 3-methyl substituent) is a mixture of 60% of 1*H* and 40% of 2*H*.[21] This result is valid for different solvents ($CDCl_3$, DMSO-d_6, THF-d_8) and different temperatures (170 K and 300 K).[21] Theoretical calculations on the tautomerism of **1c** also favor the 1*H*-tautomer for the isolated molecule.[22] The 6-methyl-4,5,6,7-tetrahydro-1(2)*H*-indazole isomer of **1c** is a 50/50 mixture of both tautomers.[23] Based on these publications,[21-23] it is possible to estimate the ^{13}C NMR signals of the "tautomeric carbons", C3 and C-7a of 4,5,6,7-tetrahydroindazole (Scheme 4).

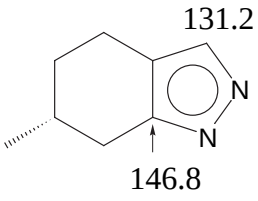
Assuming that the substituents on the carbocycle do not affect these chemical shifts, it is possible to estimate, by interpolation, the percentages of tautomers. The differences between pairs of diasteremers are small enough to be used in the calculations, thereof we have used averaged values for **2c**/**2d** and **4c**/**4d**.



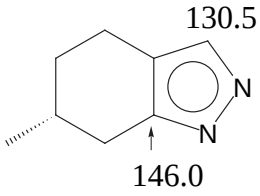
1*H*-tautomer



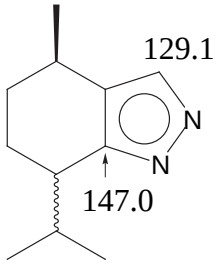
2*H*-tautomer



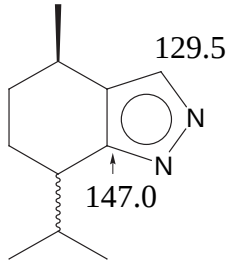
1c, Exp.



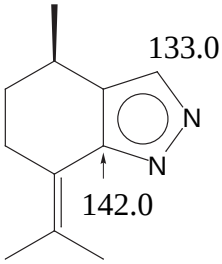
1c, Calc.
55% 1*H*



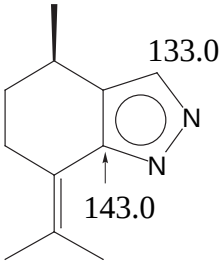
2c, **2d**
Exp. Average



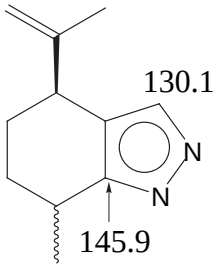
2c, **2d**
Calc. 45% 1*H*



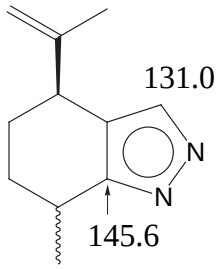
3c, Exp.



3c, Calc.
80% 1*H*



4c, **4d**
Exp. Average



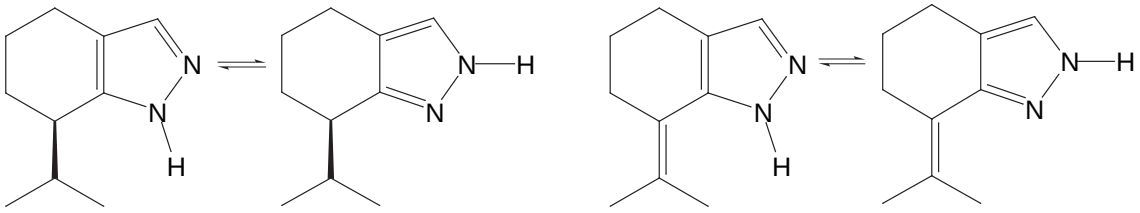
4c, **4d**
Calc. 60% 1*H*

Scheme 4

Since in no case angular strain exists, the Mills-Nixon effect cannot be used to discuss the percentages (the MN effect favors the 2*H*-tautomer).[21-24] To explain these data we selected the most extreme cases, where the saturation of the exocyclic double bond, moves the percentage of 1*H*-tautomer from 80% (**3c**) to 45% (**2c**,**2d**).

To avoid unnecessary complications, the B3LYP/6-31G* calculations[25,26] were carried on compounds lacking the 4-methyl group, thus avoiding stereochemical problems: saturated **6** and unsaturated **7** (Scheme 5). In the case of **6**, the 2*H* tautomer is the most stable (ΔG = -0.31 kcal mol^{-1}) while in the case

of **7**, the contrary is true (ΔG = 0.07 kcal mol^{-1}). These differences correspond at 25°C to 37% of 1*H* for **6** (exp. **2c**,**2d** 45% 1*H*) and 53% of 1*H* (exp. **3c** 80% 1*H*), thus, taking into account that the calculations correspond to the gas phase while the experiments have been carried out in solution, the agreement is acceptable.



6, 1*H* **6**, 2*H* **7**, 1*H* **7**, 2*H*

Scheme 5

Azine derived from 5b. The ^{1}H and ^{13}C chemical shifts of the hydroxymethylenecarvone azine (**5e**) are reported in the experimental part. This compound could exist in several isomers and tautomers, like the Schiff bases derived from β-diketones.[27] Nonconjugated tautomers can be excluded both from the ^{1}H and ^{13}C NMR spectra. The proton at 14.50 ppm belongs to an intramolecular hydrogen bond and it is coupled to H-11 (8.8 Hz), a characteristic that only the tautomer represented in Scheme 2 can explain. On the other hand, the present NMR spectral experiments do not allow to determine the relative configuration at C-5.

EXPERIMENTAL

To a suspension of two equivalents of sodium in freshly distilled ether (250 mL) were added 5 g of the monoterpenic ketone and 1.5 equivalents of ethyl formate. After 1 h, 1.5 mL of dry ethanol was added and the reaction mixture keep overnight under stirring. Then 1 mL of ethanol was added and after 2 h, 30 mL of water was added. The β-keto aldehyde was extracted with ether (2 x 100 mL) and the ether solution washed with water. The aqueous phases were mixed, acidified with aqueous 33% HCl to pH = 1 and then extracted with ether. The ethereal solutions mixed, dried over magnesium sulfate, evaporated and the residue was purified by column chromatography (silica gel, eluent CH_2Cl_2). The compounds (0.019 mmol) were immediately used; for this, they were dissolved in 20 mL of methanol and 2.5 equivalents of hydrazine monohydrate (64-65% of N_2H_4) were added dropwise. Solid compounds precipitate, liquid ones were purified by column chromatography (silica gel, eluent CH_2Cl_2). The following tetrahydroindazoles were obtained (yields between parentheses) :

(6*R*)-6-Methyl-4,5,6,7-tetrahydro-1(2)*H*-indazole (**1c**), mp 102 °C (65%), lit.,[1] mp 100-101 °C (79%).

A mixture of (4*R*,7*S*)-4-methyl-7-(1-methylethyl)-4,5,6,7-tetrahydro-1(2)*H*-indazole (**2c**, 70%) and (4*R*,7*R*)-4-methyl-7-(1-methylethyl)-4,5,6,7-tetrahydro-1(2)*H*-indazole (**2d**, 30%), oil (72%), lit.,[2] $bp_{0.09}$ 100-101 °C (83%).

(4*R*)-4-Methyl-7-(1-methylethylidene)-4,5,6,7-tetrahydro-1(2)*H*-indazole (**3c**), oil (62%), lit.,[5] $bp_{0.3}$ 117-118 °C (68%).

A mixture of (4*S*,7*R*)-4-isopropylidene-7-methyl-4,5,6,7-tetrahydro-1(2)*H*-indazole (**4c**, 60%) and (4*S*,7*S*)-4-isopropylidene-7-methyl-4,5,6,7-tetrahydro-1(2)*H*-indazole (**4d**, 40%), white solid mp 167°C (overall yield: 54%). Anal. Calcd for $C_{11}H_{16}N_2$, C, 74.96; H, 9.15; N, 15.89. Found: C, 75.03; H, 9.22; N, 15.71.

Hydroxymethylenecarvone azine (**5e**), oil (14%). Anal. Calcd for $C_{22}H_{28}N_2O_2$, C, 74.97; H, 8.01; N, 7.95. Found: C, 74.83; H, 7.88; N, 8.05. ^{1}H NMR ($CDCl_3$): 1.67 (3H, br s, H-7), 1.82 (3H, q, *J* = 1.8 Hz, H-9), 2.40 (2H, m, H-4), 3.24 (1H, br t, *J* = 7.2 Hz, H-5), 4.76 (1H, m, H-10), 4.82 (1H, quint, *J* = 1.4 Hz, H-10), 6.47 (1H, tq, *J* = 4.4 and 1.4 Hz, H-3), 7.42 (1H, d, *J* = 8.8 Hz, H-11), 14.50 (1H, d, *J* = 8.8 Hz, NH). ^{13}C NMR ($CDCl_3$): 15.47 (C-7), 19.67 (C-9), 29.15 (C-4), 41.83 (C-5), 109.73 (C-6), 113.73 (C-10), 134.62 (C-2), 141.20 (C-3), 145.69 (C-8), 169.23 (C-11), 189.40 (C-1).

^{1}H and ^{13}C NMR spectroscopy

NMR spectra were recorded on a Bruker AMX-400 spectrometer in $CDCl_3$ solutions. TMS was used as standard in both ^{1}H and ^{13}C NMR spectral measurements. 1D-HOHAHA[28] experiments were obtained with Gaussian shaped pulses for semi-selective excitation of selected protons. For gradient-selected two-dimensional experiments, an inverse probehead incorporating a shielded Z-gradient was used. The gradients were shaped by a waveform generator and were amplified by a Bruker B-AFPA-10 amplifier. Gs-COSY,[29] gs-HMQC,[30] and gs-HMBC[31] sequences were obtained from standard Bruker software.

Ab initio calculations

All the calculations were carried out at the B3LYP/6-31G* computational level using the Gaussian-98 series of programs.[32] The ΔG of the compounds have been calculated using the unscaled ZPE (zero-point error) and the thermal corrections. The four reported structures were minima as verified by the second derivatives.

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