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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2119–2123

Synthesis of *trans*/*cis* 4-substituted 3-furyl-2-phenethyltetrahydroisoquinolin-1-ones: conformation of the *trans*-4-(pyrrolidinylcarbonyl) derivative

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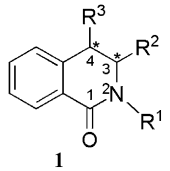
Received 13 December 2005; revised 18 January 2006; accepted 25 January 2006
Available online 13 February 2006

Abstract—The title compounds were synthesized starting from homophthalic anhydride and an imine. The amides obtained showed unexpected values for $^{3}J_{3,4}$ that cannot be used to deduce their configuration and conformation. This problem was resolved for one representative compound (the 4-(pyrrolidinylcarbonyl) derivative) by means of detailed NMR studies, X-ray diffraction and theoretical calculations. The compound has the trans configuration. In the solid state, its conformation is with *dipseudoaxial* (*aa*) oriented substituents at positions 3 and 4. In different solvents and in the gas-phase, the majority of the data reveal that the observed value of $^{3}J_{3,4}$ results from an equilibrium of the *ee* and *aa* conformers.

Compounds containing a tetrahydroisoquinoline fragment display a broad spectrum of biological properties including antitumor, antibacterial, anti-allergic, and psychotropic activities.[1] The same fragment is present in various natural alkaloids.[2] The tetrahydroisoquinolines have trans and cis forms when C-3 and C-4 are stereogenic centers. These two diastereomers, as racemates in relevant conformations, have different properties and pharmacological activities. Investigation of the correlation between structure and pharmacological activity is important from the practical point of view. This is the reason for the growing interest in the synthesis of new tetrahydroisoquinolines by different methods and the study of their stereochemical properties.[3] An important method for the preparation of compounds of type **1** is the reaction between homophthalic anhydride and an imine[4] that can be directed towards the trans or cis isomer.[5] The recent increased application of X-ray analysis in combination with various NMR techniques and theoretical calculations permits a deeper insight into stereochemistry that cannot be obtained in special cases[6] on the basis of empirically deduced criteria and classical conformational analysis.



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In this study, we synthesized some tetrahydroisoquinolines (Scheme 1) using, in the first step, the reaction between homophthalic anhydride **2** and an imine **3** with which we have much experience.[5a,7] Some of the compounds prepared, namely **6a**–**g**, showed unexpected ^{1}H NMR properties that made us study in detail the configuration and conformation under different conditions of one of these compounds, **6a**. The study is based on the experimental NMR data obtained by ^{1}H and ^{13}C NMR, COSY, HSQC and HMBC experiments, X-ray diffraction, and ab initio and DFT calculations.

Keywords: *trans*- and *cis*-Tetrahydroisoquinoline; Carboxamides; Conformational equilibrium; Ab initio and DFT calculations; Crystal structure; Dynamic NMR.
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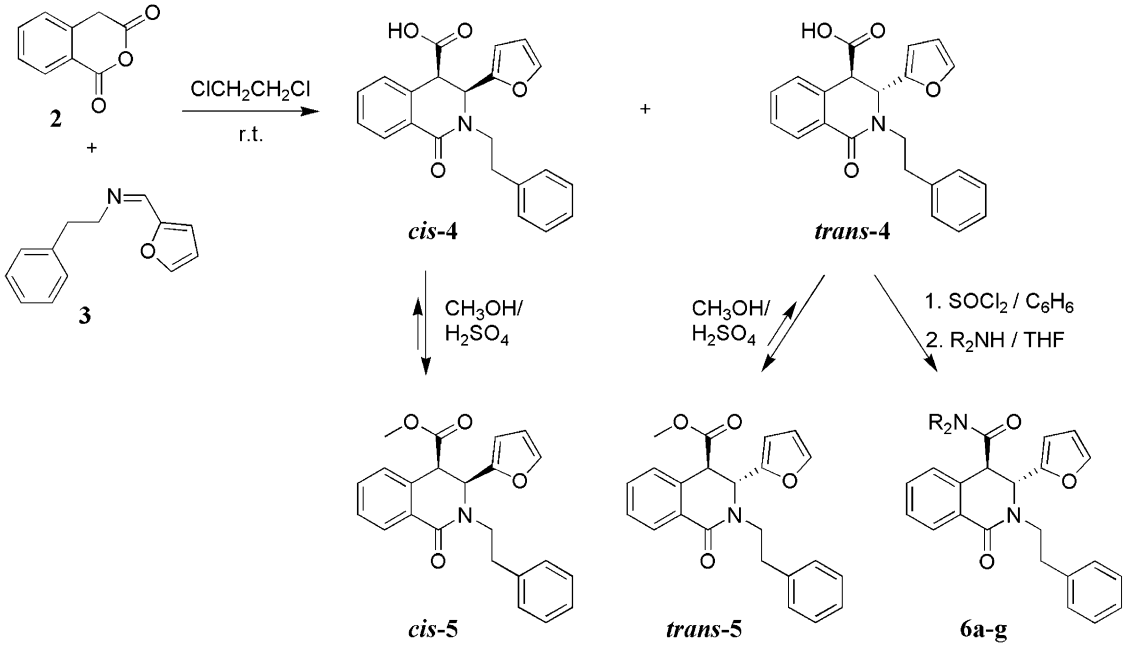
doi:10.1016/j.tetlet.2006.01.123



Scheme 1. Synthesis of diastereomeric acids **4** and esters **5** and amides *trans*-**6a**–**g** (for each compound only one of the enantiomers is shown).

Recently, we have used extensive transformations similar to those given in Scheme 1 to prepare tetrahydroisoquinolines of pharmaceutical interest. It is worth noting that the targets for this study, **6a**–**g**, contain four pharmacophoric groups: the lactam-amide fragment and phenethyl, furyl and heterocyclic amino groups. The reaction between **2** and the imine **3** was conducted in dichloroethane at room temperature to ensure kinetic control of the reaction and preparation of both diastereomeric acids **4** (trans:cis 52:22). The transformations of acids *trans*-**4** and *cis*-**4** were achieved using methods that do not affect the stereogenic centers in the molecules. The acids *trans*-**4** and *cis*-**4** were esterified with methanol/H_2SO_4 yielding the esters *trans*-**5** and *cis*-**5**. The greater quantity of *trans*-**4** available was the reason for studing its transformations into various heterocyclic amides (**6a**–**g**) which were obtained in good yields via the acid chloride[8] of *trans*-**4** and its subsequent reaction with various secondary cyclic amines (Fig. 1).[9]

The configuration and conformation of compounds **4**–**6** were established on the basis of the following empirically derived criterion of the value of the vicinal coupling constant ($^3J_{3,4}$) between the H-3 and H-4 atoms in ^{1}H NMR spectra: (a) values of 0–2.5 Hz correspond to a trans configuration and a favored conformation in solution with *dipseudoaxially* (*aa*) oriented substituents at C-3 and C-4, (b) values of 10–12 Hz suggest a trans configuration with *dipseudoequatorial* (*ee*) substituents, and (c) values of 5.5–6.5 Hz suggest a cis configuration and two difficult to differentiate conformations (*ea* and *ae*).[4,10,11]

In the ^{1}H NMR spectra of acids *trans*-**4** and *cis*-**4**, the values of $^3J_{3,4}$ were 1.6 and 5.6 Hz, respectively. For the esters *trans*-**5** and *cis*-**5** the $^3J_{3,4}$, values were 1.7 Hz and 5.5 Hz, respectively. For compounds **6a**–**g**, the constants $^3J_{3,4}$ varied in the range 6.5–7.5 Hz in $CDCl_3$. On the basis of these values of $^3J_{3,4}$, the cis configuration should be assumed for the amides **6a**–**g** although the compounds were prepared from *trans*-**4** and an inversion of its configuration is not expected. To elucidate this point, we focused our attention on a detailed study of one of the amides, namely 4-[(pyrrolidine-1-yl)-carbonyl]-3-furyl-2-phenethyl-1,2,3,4-tetrahydroisoquinolin-1-one **6a**.

In the ^{1}H NMR spectrum of **6a** in $CDCl_3$, a coupling constant $^3J_{3,4}$ of 6.7 Hz was observed.

A possible explanation for the intermediate value of $^3J_{3,4}$ could be that the compound has a trans-configuration and exists in solution as a mixture of conformers with *dipseudoequatorial* (*ee*) and *dipseudoaxial* (*aa*) substituents at C-3 and C-4, represented in approximately equal amounts. According to the data from the NOE difference spectra in $CDCl_3$ (Fig. 2), which reveals the proximity of two series of protons: (a) H-3 and H-4,

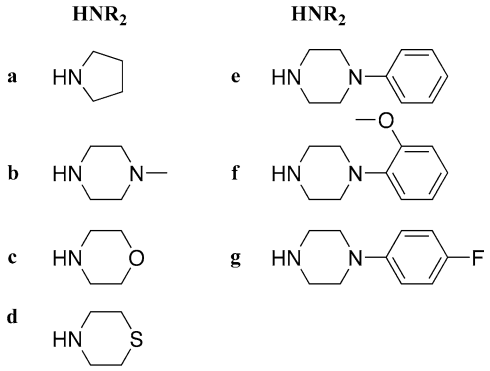


Figure 1. Secondary amines for synthesis of amides **6a**–**g**.

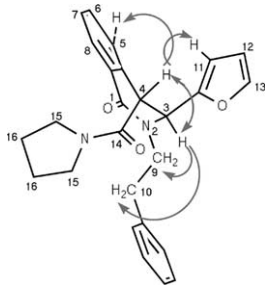


Figure 2. Representative NOE interactions in the *dipseudoaxial* (*aa*) conformer of compound **6a**.

H-9 and H-10, and (b) H-4 and H-3, H-5, H-11 and H-15, the trans configuration of **6a** is plausible.

The structure of compound **6a** in the solid state was characterized by a single-crystal X-ray[12] diffraction analysis proving unequivocally its trans configuration. As a racemic mixture, **6a** is composed of equal quantities of the *R*,*R* enantiomer (Fig. 3) and *S*,*S* enantiomer in the asymmetric unit. In both enantiomers, all the aromatic rings are nearly planar, the dihydropyridinone ring adopts a twist conformation, and the pyrrolidine ring shows an envelope conformation. The H atoms were placed in idealized positions (C–H = 0.93–0.97 Å) and were constrained to ride on their parent atoms with $U_{iso}(H) = 1.2\ U_{eq}(C)$. Friedel-pair reflections were merged, since the anomalous scattering effects were negligible. Both enantiomers are connected via intermolecular interactions: $C–H_{furyl}\cdots\pi$ (from the isoquinoline moiety) and weak $C–H_{furyl}\cdots O$ (from the lactone carbonyl). As a result, almost centrosymmetric dimer units were formed. The data show that **6a** exists only in the *aa* conformation.

The geometries of both conformers of *trans*-**6a** (*dipseudoequatorial* and *dipseudoaxial*) were elucidated by calculations at HF/6-31G**, HF/6-31+G* and B3LYP/6-31+G* levels. The calculations were carried out using the PC GAMESS version[14] of the GAMESS (US) quantum chemistry package.[15] To obtain more accurate energies, single-point calculations at MP2/6-31G**//HF/6-31G** level of theory were performed (Table 1). In all cases, the *aa* conformer was found to be more stable. The energy difference between *aa* and *ee* conformers is in the range 2.06–2.92 kcal mol^{-1} depending on the calculation level. The predicted geometry of the *aa* conformer is very similar to the actual structure determined by X-ray analysis. To estimate the effect of the polarity of the solvent on the relative stabilities of the conformers, we applied the IPCM method[16] as implemented in the GAUSSIAN 03[17] suite of programs at HF/6-31G** level for the geometries optimized at the same level of theory (IPCM/HF/6-31G**//HF/6-31G**) in $CHCl_3$ and DMSO. The energy difference between the conformers increases on going from gas-phase (2.06 kcal mol^{-1}) to $CHCl_3$ (2.33 kcal mol^{-1}) and to the more polar DMSO (2.40 kcal mol^{-1}). The geometry of both conformers was optimized using PCM[18] at B3LYP/6-31+G* level in $CHCl_3$ solvent. The energy difference between the conformers decreased to 1.93 kcal mol^{-1}.

Table 1. Relative energies (kcal mol^{-1}) of **6a** in the gas-phase and solvents

Levels of theory	*aa*	*ee*
HF/6-31G**	0.00	2.06
*IPCM/ HF/6-31G**(CHCl$_3$)*[a]	0.00	2.33
*IPCM/ HF/6-31G**(DMSO)*[a]	0.00	2.40
MP2/6-31G**//HF/6-31G**	0.00	2.36
HF/6-31+G*	0.00	2.92
HF/6-31+G*+ZPE	0.00	2.95
B3LYP/6-31+G*	0.00	2.19
PCM/ B3LYP/6-31+G(CHCl$_3$)*[b]	0.00	1.93

[a] Single point calculation.
[b] Structure optimization at this level.

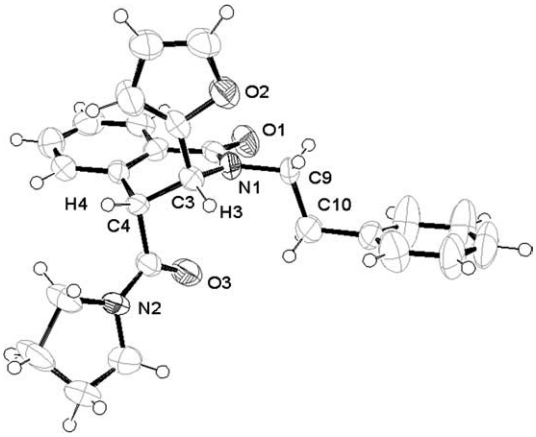


Figure 3. The structure of the *R*,*R* enantiomer. The program ORTEP3[13] was used for drawing the molecule.

The NMR chemical shieldings and coupling constants were calculated using the GIAO (gauge-including atomic orbitals) approach[19] implemented in GAUSSIAN 03 at HF/6-31G** and B3LYP/6-31+G* levels of theory. In order to compare with the experimental values, the calculated absolute shieldings were transformed to chemical shifts using the reference compound tetramethylsilane (TMS): $\delta = \delta_{calc}(TMS) - \delta_{calc}$. Both $\delta_{calc}(TMS)$ and δ_{calc} were evaluated with the same method and basis set (Table 2).

The values of the theoretically calculated coupling constant $^3J_{3,4}$ for *ee* and *aa* conformers were 11.4 and 1.9 Hz, respectively. The experimental value of $^3J_{3,4}$ (6.7 Hz) corresponds to a practically equal population

Table 2. Experimental and calculated chemical shifts and coupling constant $J_{3,4}$

Solvent	$^3J_{3,4}$ (Hz)	Chemical shift (ppm)	
		H-3	H-4
$CDCl_3$	6.7	5.14	4.53
CD_2Cl_2	4.7	5.03	4.46
DMSO-d_6	2.0	5.26	4.50
GIAO B3LYP/6-31+G*	1.9[a]; 11.4[b]	5.62[a]; 4.81[b]	3.97[a]; 4.52[b]

[a] Dipseudoaxial conformer (*aa*).
[b] Dipseudoequatorial conformer (*ee*).

of both conformers (*ee*:*aa* = 50.4:49.6) but this result does not correlate to their energy difference (Table 1). The experimental values of $^3J_{3,4}$ in $CDCl_3$, CD_2Cl_2, and DMSO-d_6 decrease from 6.7 to 2.0 Hz (Table 2). The value of the B3LYP calculated constant of the *aa* conformer is in good agreement with the value of the experimental constant in DMSO-d_6.

The possibility for equilibrium between the *ee* and *aa* conformers of *trans*-**6a** was studied by dynamic NMR. The spectra were recorded at six different temperatures in the temperature range from 300 to 190 K in CD_2Cl_2. It was found that the width and the shape of the spectral lines did not show significant temperature dependence. In fact we did not observe separate signals for the two conformers in the NMR spectra even at the lowest temperature. The variable temperature spectra also showed that the value of the $^3J_{3,4}$ constant decreases from 4.7 Hz at 300 K to 2.7 Hz at the lowest temperature of 190 K. This observation can be explained with a possible shift of the equilibrium to the more stable *aa* conformer. The results obtained from the dynamic NMR study probably imply that the possible dynamic conversion between the two conformers has very low activation energy and is fast with respect to the NMR spectral timescale. The dynamic process can be interpreted for instance as a fast flip between the *aa* and *ee* forms of *trans*-**6a** as a result of a partial ring inversion and/or inversion at the piperidinone N atom.

In conclusion, we point out that the presence of a conformational equilibrium for **6a** and therefore for **6b–g** when the compounds do not have a preferred conformation is probably due to the unique combination of the substituents in positions 2, 3 and 4 having different effective volumes. More precisely, the combination of 2-phenethyl and 4-amide groups is crucial. A combination of other groups (for instance benzyl or cyclohexyl[20a]) at position 2- and 4-amide groups does not result in intermediate values of $^3J_{3,4}$. Of the few hundred tetrahydroisoquinolines of type **1** synthesized in our laboratory (a),[4,5a,6b,7,8,20] **6a–g** are the only few compounds showing intermediate values of $^3J_{3,4}$. It is worth noting that when the assignment of configuration is not straightforward, additional methods other than ^{1}H NMR should be applied.

Acknowledgements

Thanks are due to Johnson & Johnson, R&D, Janssen Pharmaceutica, Belgium, for financial support of the project, to Dr. Benoit Champagne, Notre-Dame de la Paix University, Namur, Belgium, for help with computing facilities and to Professor Ivan Pojarlieff, Bulgarian Academy of Sciences, for useful comments on the manuscript.

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9. All new compounds were purified by column chromatography on silica gel (see below for the eluent) and characterized on the basis of NMR and microanalytical data. Data for selected compounds: Ester *trans*-**5**: R_f 0.58 (toluene/EtOAc 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.91–3.04 (m, 2H, 10-H), 3.20–3.29 (m, 1H, 9-H), 3.68 (s, 3H, CO_2CH_3), 4.17 (d, 1H, 4-H, $J = 1.68$ Hz), 4.26–4.36 (m, 1H, 9-H), 5.42 (s, 1H, 3-H), 5.90–5.92 (m, 1H, 12-H), 6.14–6.16 (m, 1H, 11-H), 7.17–7.49 (m, 9H, 13-, 6-, 5-, 7-, Ph-H), 8.11–8.14 (m, 1H, 8-H); ^{13}C NMR (60 MHz, $CDCl_3$): δ 34.1 C-9, 48.1, 48.9 C-10, 52.9, 56.4, 107.6 C-12, 110.4, 126.3, 128.0, 128.4, 128.5 (2C), 128.8 (3C), 129.2, 132.0, 132.5, 138.8, 142.4, 151.9, 163.2, 170.5. Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64. Found: C, 73.55; H, 5.73. Ester *cis*-**5**: R_f 0.55 (toluene/EtOAc 4:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.84–3.08 (m, 2H, 10-H), 3.14–3.26 (m, 1H, 9-H), 3.71 (s, 3H, CO_2CH_3), 4.30 (d, 1H, 4-H, $J = 5.5$ Hz), 4.24–4.34 (m, 1H, 9-H), 4.76 (d, 1H, 3-H, $J = 5.5$ Hz), 5.89 (d, 1H, 12-H, $J = 3.3$ Hz), 6.16–6.18 (m, 1H, 11-H), 7.20–7.50 (m, 9H, 13-, 6-, 5-,7-, Ph-H), 8.16–8.20 (m, 1H, 8-H). ^{13}C NMR (60 MHz, $CDCl_3$): δ 34.4 C-9, 47.5, 48.7 C-10, 52.2, 56.8, 108,9, 110.3, 126.5, 127.0, 128.2, 128.6 (2C), 128.8 (3C), 132.0, 132.8, 139.0, 142.6 C-13, 150.1, 163.7 C-1, 169.4 C-15. Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64. Found: C, 73.20; H, 5.56. Compound **6a**: R_f 0.28 (hexane/EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.82–2.08 (m, 4H, 16-H), 2.83–2.90 (m, 2H, 10-H), 3.05–3.17 (m, 1H, 9-H), 3.35–3.64 (m, 4H, 15-H), 4.07–4.19 (m, 1H, 9-H), 4.53 (d, 1H, 4-H, $J = 6.7$ Hz), 5.14 (d, 1H, 3-H,

$J = 6.7$ Hz), 6.17 (d, 1H, 12-H, $J = 3.3$ Hz), 6.30 (dd, 1H, 11-H, $J = 3.3$, 1.9 Hz), 6.99–7.06 (m, 1H, 5-H), 7.12–7.31 (m, 5H, Ph-H), 7.36–7.46 (m, 3H, 13-, 6-, 7-H), 8.16–8.20 (m, 1H, 8-H); ^{13}C NMR (60 MHz, $CDCl_3$): δ 24.3 (C-16), 26.2 (C-16), 34.0 (C-10), 46.1 (C-15), 47.0 (C-15), 47.5 (C-4), 47.6 (C-9), 57.0 (C-3), 109.4 (C-12), 110.7 (C-11), 126.2 (C-5), 126.3, 128.0, 128.4 (2C), 128.5, 128.8 (2C), 129.5, 134.5, 132.0 (C-7), 139.5, 142.6 (C-13), 151.4, 163.7 (C-1), 168.3 (C-14). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32. Found: C, 75.66; H, 6.10.

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