

Synthesis and Crystal Structure of Two Nitro-Regioisomers of cis-4-(4-Methoxyphenyl)-3-Methyl-2-Phenyl-1,2,3,4-Tetrahydroquinoline

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Abstract. Here we synthesized two nitro regioisomers of cis-4-(4-methoxyphenyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline via the “one pot” three-component imino Diels-Alder reaction catalyzed by $\text{BF}_3 \cdot \text{OEt}_2$ and completed its structural characterization using the single crystal X-ray diffraction technique and other spectroscopic methods. To monitor the purity of the products and the composition of the reaction mixtures we used thin layer chromatography, and isolated and purified the products by column chromatography. Then using nuclear magnetic resonance (NMR) and mass spectrometry (MS) identified the substances. We collected X-ray diffraction data for crystal characterization by using a Bruker AFC7S Mercury diffractometer with $\text{Mo-K}\alpha$ radiation ($\lambda = 0.71073\text{\AA}$) at room temperature. The structures of these regioisomers were confirmed by ^1H NMR and ^{13}C NMR studies and studied their crystal structure using single crystal X-ray diffraction technique. The spectroscopy analyses (NMR, GC-MS and X-ray diffraction) provided a complete characterization and enabled the correct stereochemistry for the tetrahydroquinoline ring. We determined the molecular packing for the 5-nitro regioisomer 4 is the product of the combination of intermolecular hydrogen bonds and van der Waals interactions, while for 7-nitro regioisomer 3 is mainly due to weak intermolecular van der Waals interactions and $\text{N}-\text{H} \cdots \pi$.

Keywords: Tetrahydroquinolines, Imino Diels-Alder reaction, nitro-regioisomers, single crystal X-ray diffraction

Síntesis y estudio de la estructura cristalina de dos nitro regioisómeros de la cis-4-(4-metoxifenil)-3-metil-2-fenil-1,2,3,4-tetrahydroquinolina. Resumen. Dos nitro-regioisómeros de la molécula cis-4-(4-metoxifenil)-3-metil-2-fenil-1,2,3,4-tetrahydroquinolina fueron preparados vía una síntesis one-pot de tres componentes basada en la reacción de cicloadición imino Diels-Alder catalizada por $\text{BF}_3 \cdot \text{OEt}_2$. Su completa caracterización estructural se llevó a cabo usando la técnica de difracción de rayos-X de monocristal y métodos espectroscópicos. La pureza de los productos y la composición de las mezclas de reacción fueron monitoreadas por cromatografía en capa fina (CCD). Los productos fueron aislados y purificados usando cromatografía en columna. Las sustancias fueron identificadas usando resonancia magnética nuclear (RMN) y espectrometría de masas (EM). Los datos para la caracterización por difracción de rayos-X fueron coleccionados usando un difractómetro Bruker AFC7S Mercury con radiación de $\text{Mo-K}\alpha$ ($\lambda = 0.71073\text{\AA}$) a temperatura ambiente. Las estructuras de los regio-isómeros fueron confirmadas por ^1H RMN y ^{13}C RMN y la estructura cristalina fue estudiada usando la difracción de rayos-X de monocristal. El análisis espectroscópico (RMN, EM y difracción de rayos-X) mostró una completa caracterización y permitió establecer la correcta estereoquímica para el anillo tetrahydroquinolinico. El empaquetamiento molecular en el cristal para el regioisómero 5-nitro 4 es producto de la combinación de enlaces de hidrógeno intermoleculares e interacciones de van der Waals, mientras que en el 7-nitro regioisómero 3 el empaquetamiento se debe principalmente a interacciones intermoleculares débiles de tipo van der Waals y $\text{N}-\text{H} \cdots \pi$.

Resumo. Dois nitro regioisómeros da molécula cis-4-(4-metoxifenil)-3-metil-2-fenil-1,2,3,4-tetrahydroquinolina foram preparados através de uma síntese de um só recipiente de três componentes com base na reação de imino Diels-Alder cicloadição catalisada $\text{BF}_3 \cdot \text{OEt}_2$ e sua completa caracterização estrutural foi realizada usando a técnica de difração cristalografia de raios X, e outros métodos espectroscópicos. A pureza do produto e a composição das misturas reacionais foram monitorizadas por cromatografia em camada fina (CCD). Os produtos foram isolados e purificados utilizando cromatografia em coluna. As substâncias foram identificadas por ressonância magnética nuclear (RMN) e espectrometria de massa (EM). Os dados para caracterização por difração de raios X foram coletados usando um Bruker AFC7S Mercury difratômetro com $\text{Mo-K}\alpha$ radiação ($\lambda = 0,71073\text{\AA}$) a temperatura ambiente. As estruturas dos regioisómeros foram confirmadas por ^1H RMN e ^{13}C RMN a estrutura de cristal foi investigada usando difração de raios X de cristal único. As análises espectroscópicas (RMN, EM e difração de raios-X) demonstraram uma completa caracterização e permitiram estabelecer a estereoquímica correta de anel tetrahydroquinolinico. O empacotamento molecular no cristal para 5-nitro regioisómero 4 é derivado de uma combinação de ligações de hidrogênio intermoleculares e interações de van der Waals, e ao 7-nitro regioisómero 3 embalagens é principalmente devido a interações intermoleculares fracas do tipo van der Waals e $\text{N}-\text{H} \cdots \pi$.

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Introduction

A great number of natural and synthetic tetrahydroquinoline compounds are core structures in many important pharmaceutical agents (Katrizky et al. 1996, Kouznetsov et al. 1998). These heterocycle compounds play a key role in bioorganic and medicinal chemistry; they exhibit a wide range of biological activity, such as, antipsychotic (Singer et al. 2005), anti-inflammatory (Calhoun et al. 1995), anti-ulcers (Uchida et al. 1989), estrogenic receptors (Chen et al. 2007, Wallace et al. 2007) and antimalarial activities (Bendale et al. 2007), among others.

Many methods have been developed for synthesis of tetrahydroquinoline derivatives (Sridharan et al. 2011). Cycloaddition reactions have proved to be the most powerful and successful reactions to construct these ring systems rapidly; while the acid-catalyzed imino Diels-Alder reaction (Povarov reaction) between 2-azadienes and electron-rich alkenes in its three-component version is one of the most powerful synthetic tools for the construction of nitrogen-containing six-membered heterocyclic compounds, including tetrahydroquinolines (Kouznetsov 2009, Glushkov et al. 2008, Buonora et al. 2001). This reaction enables the condensation of anilines, aldehydes, and electron-rich alkenes using acidic catalysts under mild conditions to obtain new substituted tetrahydroquinolines. Recently, the use of phenylpropenoid derivatives (electron-rich alkenes, e.g. *trans*-anethole) such as dienophile in this cycloaddition process has been given significant attention (He et al. 2012, Romero et al. 2011). However, little has been explored on the crystallographic study of this type of derivatives by X-ray diffraction.

Our ongoing research program has focused on the chemistry and bioactivity of tetrahydroquinoline derivatives (Romero et al. 2012) and its single crystal X-ray crystallographic study, to explain the stereochemistry of the imino Diels-Alder reaction and the performance of this material in the crystalline state (Bermudez et al. 2011). In this paper, we will show an easy and simple preparation of two constitutional isomers of nitro-tetrahydroquinoline derivatives, compounds *cis*-4-(4-methoxyphenyl)-3-methyl-7-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline 3

and *cis*-4-(4-methoxyphenyl)-3-methyl-5-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline 4 using the three-component imino Diels-Alder cycloaddition methodology (Kouznetsov 2009), this reaction that enables the generation of 1,2,3,4-tetrahydroquinoline derivatives with high structural diversity. We have also determined the crystal structure of these compounds using X-ray techniques, confirming their spectral characterization and obtaining detailed information about their molecular conformation.

Materials and methods

Infrared (IR) spectra were recorded on a Lumex Infracum FT-02 spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer (400 MHz ^1H NMR and 100 MHz ^{13}C NMR), using CDCl_3 as the solvent. Trimethylsilyl (TMS) was used as an internal standard. Chemical shifts (δ) and J values are reported in ppm and Hz, respectively. A Hewlett Packard 5890a Series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector with an HP MS ChemStation Data system was used for MS identification at 70eV using a 60m capillary column coated with HP-5 [5% phenylpoly (dimethylsiloxane)]. Melting points (uncorrected) were measured on a Fisher Johns melting point apparatus. X-ray diffraction data were collected using a Bruker AFC7S Mercury diffractometer with graphite-monochromated Mo-K_α radiation ($\lambda = 0.71073\text{\AA}$) at room temperature. Crystals with dimensions 0.53 x 0.48 x 0.43mm (comp. 3) and 0.55 x 0.48 x 0.45mm (comp. 4) were used. Data having theta less than or equal to 25° were integrated and the structure was solved by the direct method using the SHELXS-97 program (Sheldrick 2008), which was refined by the full-matrix least-squares method using the SHELXS-97 program. Crystal data and experimental details are listed in tables 1, 2 and 3 respectively. All H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C-H distances of 0.96\AA and $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$. The H atom bonded to N was located from Fourier difference map. The reaction progress was monitored using thin layer chromatography (TLC) on a Silufol UV 254 TLC aluminum sheet. Column

chromatography was carried out using Silica gel (230-400 mesh). All reagents were purchased from Sigma and Aldrich Chemical Co. and used without further purification.

Synthesis of Two Nitro-Regioisomers of *cis*-4-(4-methoxyphenyl)-3-Methyl-2-Phenyl-1,2,3,4-Tetrahydroquinoline. General procedure: The general procedure was previously described by Kouznetsov et al. (2007) and performed as follows: A mixture of *m*-nitroaniline (2.90mmol) and benzaldehyde (3.19mmol) in anhydrous CH₃CN (15mL) was stirred for 30 min. at room temperature. BF₃·OEt₂ (2.90mmol) was then added. A solution of commercial *trans*-anethole (3.48mmol) in CH₃CN (10mL) was added dropwise over a period of 20min. The resulting mixture was stirred at 70°C for 10 hours. Once the reaction was completed, as indicated by the TLC, the reaction mixture was diluted with water (30mL) and extracted with ethyl acetate (3 times \times 15mL). The organic layer was separated and dried (Na₂SO₄) then concentrated *in vacuo*. The crude product was purified by column chromatography using silica gel (60-120 mesh) and eluted with petroleum ether-ethyl acetate to afford the tetrahydroquinoline products, the *cis*-4-(4-methoxyphenyl)-3-methyl-7-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline 3 (8% yield) and their regioisomer, the *cis*-4-(4-methoxyphenyl)-3-methyl-5-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline 4 (yield 80%). Both compounds were obtained as a yellow solid with melting point 174-175°C and 141-142°C, respectively. Both compounds were recrystallized by slow evaporation of a dichloromethane solution.

***Cis*-4-(4-Methoxyphenyl)-3-methyl-7-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline 3:** This compound was isolated as a yellow solid with Melting point (Mp) 141-142°C (uncorrected). The molecular characterization that was carried out with infrared (IR) spectrometry showed the following characteristic signals: 3376, 1610, 1521 and 1317cm⁻¹; Mass Spectrometry (MS) gave a molecular peak *m/z* = 374 (67, M⁺); Nuclear Magnetic Resonance on protons ¹H NMR (400 MHz, CDCl₃, Me₄Si) showed δ (ppm) to be 0.59 (3H, d, *J* = 6.5 Hz, -CH₃), 2.17 (1H, m, 3-H), 3.73 (1H, d, *J* = 11.0

Hz, 2-H), 3.82 (3H, s, Ar-OCH₃), 4.17 (1H, d, *J* = 10.0 Hz, 4-H), 4.38 (1H, s, N-H), 6.66 (1H, d, *J* = 8.8 Hz, 8-H), 6.89 (2H, d, *J* = 8.6 Hz, 2'-H_{Ar}), 7.10 (2H, d, *J* = 8.6 Hz, 3'-H_{Ar}), 7.35-7.40 (7H, m, all-H_{Ar} and 6-H, 7-H); Nuclear Magnetic Resonance on Carbons ¹³C-NMR (100 Hz, CDCl₃, Me₄Si), δ (ppm), presented the following data: 158.5, 147.1, 145.4, 141.7, 134.8, 132.5, 131.2, 130.5, 128.8, 128.6, 127.7, 114.0, 111.7, 107.5, 64.8, 54.5, 50.8, 40.3, 16.3.

***Cis*-4-(4-Methoxyphenyl)-3-methyl-5-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline 4:** This compound was isolated as a yellow solid; with Melting point (Mp) 174-175°C (Uncorrected). The molecular characterization carried out by infrared (IR) spectrometry showed the following characteristic signals: 3395, 1609, 1527 and 1323cm⁻¹; Mass Spectrometry (MS) gave a molecular peak *m/z* = 374 (30, M⁺); Nuclear Magnetic Resonance on protons ¹H NMR (400 MHz, CDCl₃, Me₄Si) showed δ (ppm) to be : 0.68 (3H, d, *J* = 6.6 Hz, -CH₃), 2.03 (1H, m, 3-H), 3.75 (3H, s, Ar-OCH₃), 4.01 (1H, d, *J* = 10.2 Hz, 2-H), 4.21 (1H, d, *J* = 10.2 Hz, 4-H), 4.36 (1H, s, N-H), 6.75 (1H, dd, *J* = 8.1, 1.2 Hz, 8-H), 6.76 (2H, d, *J* = 8.7 Hz, 2'-H_{Ar}), 6.89 (1H, dd, *J* = 7.8, 1.2 Hz, 6-H), 6.98 (2H, d, *J* = 8.7 Hz, 3'-H_{Ar}), 7.08 (1H, td, *J* = 8.1, 0.6 Hz, 7-H), 7.33-7.42 (5H, m, all-H_{Ar}); Nuclear Magnetic Resonance on Carbons ¹³C-NMR (100 Hz, CDCl₃, Me₄Si), δ (ppm), presented the following data: : 158.0, 152.3, 147.8, 141.2, 135.1, 130.4, 128.6, 128.2, 127.7, 127.1, 119.4, 118.0, 114.1, 113.4, 62.6, 55.1, 48.0, 45.0, 16.1.

Results

Regioisomeric nitro-tetrahydroquinolines 3 and 4 were easily prepared via the protocol of a "one pot" three-component imino Diels-Alder reaction between *in situ* forming N-aryl aldimines and *trans*-anethole in the presence of BF₃·OEt₂, at 70°C in acetonitrile. These compounds were synthesized by cycloaddition reaction starting from the commercially available 3-nitroanilines 1, benzaldehyde 2, and *trans*-anethole, according to the literature procedure (Kouznetsov et al. 2007,

Kouznetsov et al. 2008). The required products 3 and 4 were obtained in good yields after column chromatography purification on silica gel (Figure 1).

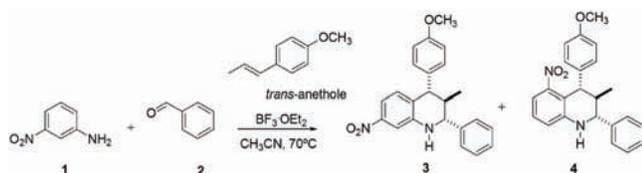


Fig. 1. Synthesis of nitro-regioisomers of tetrahydroquinolines using the three-component imino Diels-Alder reaction.

The structures of the nitro-regioisomers 3 and 4 were confirmed on the basis of analytical and spectral data using ^1H NMR and ^{13}C NMR studies and were supported by inverse-detected 2D NMR experiments. Their crystal structure was studied using single crystal X-ray diffraction technique.

Crystal data, refinement and experimental details are listed (Tables 1 and 2), respectively.

Table 1. Crystal data and refinement of the nitro-regioisomers tetrahydroquinolines (3, 4).

Crystal data and refinement	7-nitro THQ (3)	5-nitro THQ (4)
<i>Data crystal</i>		
Empirical Formula	$\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_3$	$\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_3$
Formula weight	374.43	374.43
Temperature (°C)	25	25
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$ (N°14)	$P2_1/c$ (N°14)
<i>Unit cell dimensions</i>		
<i>a</i> (Å)	19.203 (4)	7.2170 (12)
<i>b</i> (Å)	6.0446 (10)	14.026 (2)
<i>c</i> (Å)	18.336 (4)	19.484 (3)
β (°)	116.293 (4)	98.394 (4)
Volume (Å ³)	1908.1 (7)	1951.2 (6)
<i>Z</i>	4	4
Density (calculated) (Mg/m ³)	1.303	1.275
Reflections collected	3716 [$R_{\text{int}} = 0.032$]	4056 [$R_{\text{int}} = 0.054$]
Independent reflections	Full-matrix	Full-matrix
Refinement methods	least-squares on <i>F</i> ²	least-squares on <i>F</i> ²
Final <i>R</i> indices	$R_1 = 0.055$, [$I > 2\sigma(I) = 2972$ data]	$R_1 = 0.067$, $wR_2 = 0.166$

The crystal packing for the 5-nitro regioisomer 4 was the result of combinations of intermolecular hydrogen bonds of the N—H...O type and van der Waals interactions, which may lead to the supramolecular structure of the molecule.

Table 2. Selected bond lengths (Å) and bond angles (°) of the nitro-regioisomers THQs (3, 4).

Crystal data and refinement	7-nitro THQ (3)	5-nitro THQ (4)
<i>Bond lengths</i> (Å)		
O1—C21	1.372 (2)	1.366 (3)
O1—C24	1.429 (2)	1.432 (3)
N1—C10	1.390 (2)	1.387 (3)
N1—C2	1.460 (2)	1.453 (3)
N1—H1	0.9844	0.8500
C2—C11	1.511 (3)	1.513 (4)
C2—C3	1.533 (3)	1.526 (4)
C3—C4	1.542 (3)	1.546 (4)
<i>Bond angle</i> (°)		
C10—N1—C2	119.92 (15)	118.6 (2)
C10—N1—H1	117.0	113.2
C2—N1—H1	112.6	117.2
N1—C2—C11	109.52 (15)	109.7 (2)
N1—C2—C3	108.98 (14)	108.1 (2)
C11—C2—C3	113.02 (15)	113.5 (2)
N1—C2—H2A	108.4	108.4
C3—C2—H2A	108.4	108.4
C2—C3—H3A	108.3	107.7

The hydrogen bonding descriptions are listed in (Table 3).

Table 3. Hydrogen-bond geometry and Short contact data (Å, °) of the nitro-THQ 4.

D—H...A	D—H	H...A	D...A	D—H...A
N1—H1...O3i	0.85	2.36	3.197 (3)	170
C24—H24B...O1ii	0.96	2.53	3.233 (4)	130

Symmetry codes: (i) $-x+1, y+1/2, -z+1/2$; (ii) $-x, -y, -z+1$.

Crystallographic data (excluding structure factors) for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, Nos. CCDC 913850 (Comp. 3) and 913851 (Comp 4). A copy of the data can be obtained free of

charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk].

Discussion

Synthesis and Characterization: Our report is based on our experience in the synthesis of bioactive tetrahydro (quinoline) derivatives via multi-component Povarov reaction (Meléndez et al. 2008, Vargas et al. 2007). Here, we describe our synthetic and crystallographic studies on nitro-regioisomers 2, 4-diaryl-3-methyl-1,2,3,4-tetrahydroquinoline derivatives 3 and 4, synthesized by cycloaddition reaction, as shown (Figure 1). These nitro tetrahydroquinoline regioisomers were easily prepared in good yield with almost no by-products via the protocols of a “one pot” three-component imino Diels-Alder reaction. Studied tetrahydroquinolines were isolated and purified by column chromatography (SiO₂) using petroleum ether/ethyl acetate as yellow solids with defined melting points (Table 4).

Table 4. Physicochemical properties of the nitro-regioisomers tetrahydroquinoline (3) and (4).

Comp.	Mol. formula ^a	M.W. (g/mol)	M.p. (°C) ^b	Yield (%) ^c	IR $\nu_{\text{N-H}}, \nu_{\text{NO}_2}$ (cm ⁻¹)
3	C ₂₃ H ₂₂ N ₂ O ₃	374	141-142	8	3376, 1610, 1521, 1317
4	C ₂₃ H ₂₂ N ₂ O ₃	374	174-175	80	3395, 1609 1527, 1323

^a Confirmed by MS data ^b Uncorrected, ^c Isolated yield after CC.

We observed characteristic IR spectrum absorption bands in both compounds at 3395-3376 and 1610-1609cm⁻¹, assignable to the amine groups, and the nitro group signals at 1527-1521 and 1323-1317cm⁻¹, respectively. Their mass spectrum showed a molecular ion m/z : = 374 that coincided in both cases with their molecular weight (374g/mol). ¹H NMR and GC-MS analyses of the tetrahydroquinoline products showed that the structure of the unique diastereoisomer 3 and 4 detected was a *cis*-(2e, 4e) configuration. The large vicinal coupling constants $J_{2a,3a}$ and $J_{3a,4a}$ = 9.9-11.0 Hz indicate an axial-axial (*trans*) relationship, and the aryl groups on C-2 and C-4 are both pseudo-

equatorial and are in the *cis*-configuration (Figure 2). The X-ray crystallographic analysis showed that the substituents of the tetrahydroquinoline ring occupy equatorial positions, confirming that the reaction was highly diastereoselective.

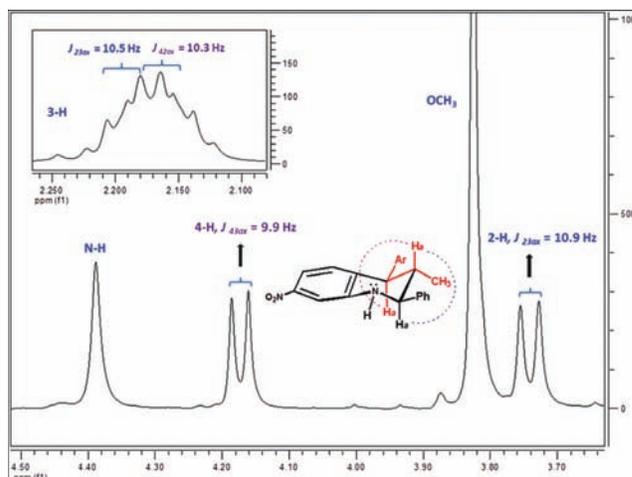


Fig. 2. Coupling between 3-H proton and 2-H and 4-H protons in 1H RMN spectra of *cis*-4-(4-methoxyphenyl)-3-methyl-7-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline.

X-Ray Diffraction Single Crystal Study: Crystals suitable for single crystal X-ray diffraction were grown from slow evaporation of a dichloromethane solution at room temperature. We collected X-ray diffraction data using a Bruker AFC7S Mercury diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073Å) at room temperature. In both case (compounds 3 and 4) data collection, cell refinement and data reduction was achieved using the CrystalClear program (Rigaku 2005). And to solve and to refine the structure, SHELXL-NT V5.1 software (Bruker 1998) was used.

The perspectives of the analyzed molecules 3 and 4 indicated that these compounds have

normal values of bond lengths and angles (**Figure 3**). We also noted also that compounds 3 and 4 are isomorphous, only with significant variations in their *a* and *b* unit-cell parameters. This difference between the two regioisomers could be due to their capability to form intermolecular hydrogen bonds through interactions between a nitro group and tetrahydroquinoline.

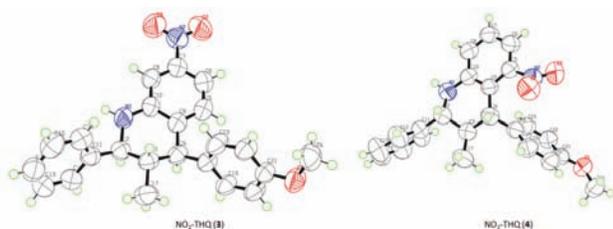


Fig. 3. The molecular structures of 7-nitro (3) and 5-nitro (4) tetrahydroquinolines, showing the atom-label scheme. Displacement ellipsoids are drawn at the 50% probability level (Farrugia 1997).

Analyzing the X-ray data, we found that the 7-NO₂ isomer 3 could form only weak van der Waals type interactions, while their 5-NO₂ regioisomer 4 was capable of organizing both van der Waals and hydrogen bond (N—H...O) interactions. It should be noted that there are three stereogenic centers in each studied compound; therefore the C2(*S*), C3(*S*), C4(*R*)-configuration was suggested for the structures of the obtained molecules. However, the centrosymmetric space group *P*2₁/*c* (N°14) indicates that the compounds are racemates, with configuration C2 (*SR*), C3 (*SR*), C4 (*RS*). The conformation for compounds 3 and 4 was imposed by the tetrahydroquinoline structural fragment, which possesses a half-chair conformation, despite some small deviations. All three substituent groups (two aryl rings and methyl) of both compounds occupy equatorial positions in the tetrahydropiperidine moiety of the quinoline core. This affirmation confirms, unequivocally, the high diastereoselectivity of the imino Diels-Alder reaction for this case.

On the other hand, the data of compounds 3 and 4 indicated that the sum of the values of angles measured between the three neighboring atoms C10—N1—H1, C2—N1—H1, and C10—N1—C2 were 349.30° and 349.00°, respectively. These

values, closer to 360°, suggest that the atom N1 of the tetrahydroquinoline ring did not completely adopt *sp*³ hybridization and tends towards an *sp*² hybridization type (Henao et al. 1999). These small deviations in N1 hybridization in the compounds are possibly due to the imminent relocation of the free electron pair in the nitrogen atom of the piperidine moiety through the aromatic ring and towards the oxygen atoms in the NO₂ group present in all molecules. Moreover, regioisomers (3) and (4) differ in bond lengths between atoms C10—N1 (1.38 and 1.39Å, respectively), these values are closer to a double bond than to a typical simple C—N bond, which has a C2—N1 bond (1.45 and 1.46Å, respectively).

The crystal packing of compound 4 was governed principally by hydrogen bond-like intermolecular interactions (Table 3). However, they also presented van der Waals interactions, such as the intermolecular N—H...O interaction [N1...O1 3.197Å] (**Figure 4**) involving the N—H of the quinoline saturated part and one oxygen atom of the NO₂ group and the intermolecular van der Waals interactions C—H...O [C24...O1 3.234Å], and C—H...C [C15...C23 3.559Å]. In contrast, compound 3 had only intermolecular van der Waals interactions. The most significant interactions were between the N1 atom and one aromatic carbon N—H...C [N1...C13 3.469Å], between C—H...O [C24...O2 3.346Å] and the C—H...O [C6...O1 3.392Å] interactions (**Figure 4**).

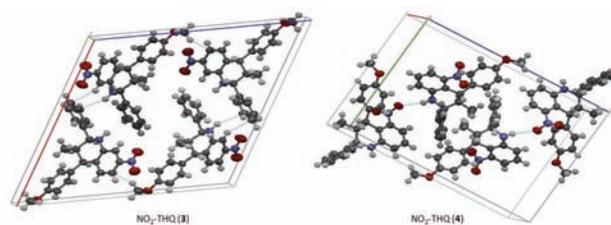


Fig. 4. Perspectives drawing of the packing arrangement in nitro-regioisomers THQ (3) and (4). Dashed lines indicate the intermolecular van der Waals interactions.

Conclusion

An easy and efficient synthetic method was employed to prepare two nitro tetrahydroquinoline

regioisomers. The spectroscopy analyses (NMR, GC-MS and X-ray diffraction) enabled a complete characterization and established the correct stereochemistry for the tetrahydroquinoline ring. The complete spectral analysis indicated an axial-axial (*trans*) relationship, and the aryl groups on C-2 and C-4 are both pseudo-equatorial and are in the *cis*-configuration. The X-ray crystallographic analysis showed that the substituents of the tetrahydroquinoline ring occupy equatorial positions, confirming that the reaction was highly diastereoselective. The molecular packing for the 5-nitro regioisomer 4 is the result of combinations of intermolecular hydrogen bonds and van der Waals interactions, while the 7-nitro regioisomer 3 maintains only intermolecular van der Waals interactions and N—H... π interactions, which also occur.

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The authors declare that no conflicts of interest exist in relation to this work.

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