Non-biaryl Atropisomers. Part 1. Configurationally Stable 1,2-Diaryl-3-methyl-1,4,5,6-tetrahydropyrimidinium Salts

María B. García, Isabel A. Perillo and Liliana R. Orelli*

Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica,
Universidad de Buenos Aires, Junín 956 (1113), Buenos Aires, Argentina
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In the present communication we describe two examples of a new kind of configurationally stable non-biaryl atropisomers in which the Ar-N bond is the chiral axis, namely 1-(*o*-nitrophenyl)-2-aryl-3-methyl-1,4,5,6-tetrahydropyrimidinium iodides **1**. Stereochemical features of such compounds are analyzed on the basis of their ^{1}H and ^{13}C one- and two-dimensional nmr spectra. A comparison is made with the corresponding amidines **2**.

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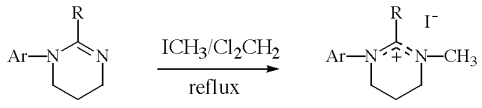
Introduction.

Literature about atropisomers is generally restricted to biphenyl and binaphthyl derivatives, some of which are widely employed as chiral ligands in enantiospecific reactions [1]. In the past few years some examples of stable non-biaryl atropisomers have also been reported [2]. Such compounds are interesting from a stereochemical viewpoint and also due to their potential employment in stereoselective reactions [3]. In the present communication we describe two examples of configurationally stable non-biaryl atropisomers, namely 1-(*o*-nitrophenyl)-2-aryl-3-methyl-1,4,5,6-tetrahydropyrimidinium salts **1** (Scheme I).

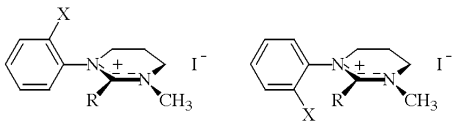
Scheme I



2 **1**

Compound 1,2	Ar	R
a	*o*-$NO_2C_6H_4$	C_6H_5
b	*o*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$

Scheme II



Spectral features of 1,2-diaryl-3-methyl-1,4,5,6-tetrahydropyrimidinium salts previously reported by us [4], in which the aryl groups are symmetrically substituted, indicate a time averaged conformation in which the heterocyclic ring is planar. In such derivatives the 1-aryl substituent presumably adopts a twisted conformation with respect to the plane of the heterocyclic ring (bisectional conformation) in order to avoid steric interaction with the vicinal 2-aryl group. An alternative conformation with the 1-aryl group coplanar to the amidinium system (coplanar conformation) can thus be discarded. When the 1-aryl group is disymmetrical, as in 1-*ortho* substituted salts, two bisectional conformations are possible, as shown in Scheme II. Due to the absence of a plane of symmetry, bisectional conformers are axially chiral compounds in which the Ar-N bond is the chiral axis. As a consequence of this, such compounds would

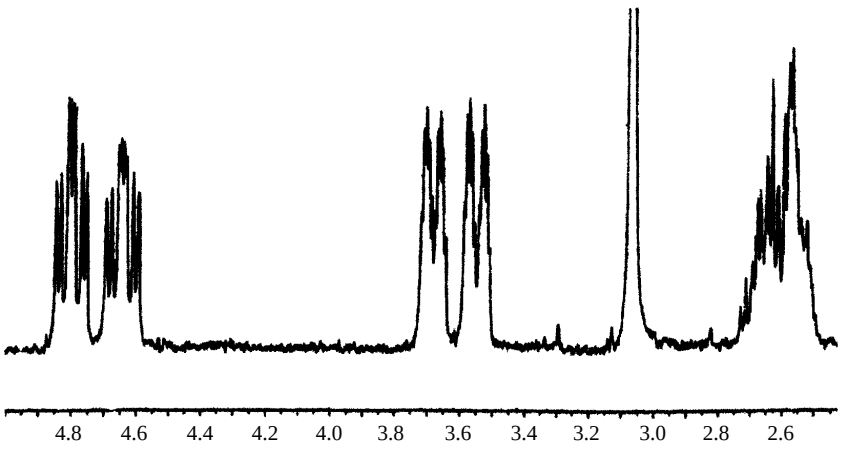
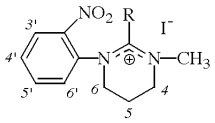
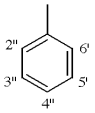
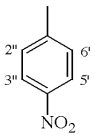


Figure. H^1 Nmr spectrum of compound **1a** (trimethylene region).

Table I

^{1}H Nmr Spectra of 1-(*o*-Nitrophenyl)-2-aryl-3-methyl-1,4,5,6-tetrahydropyrimidinium Salts **1a,b**

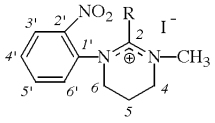


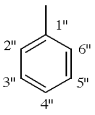
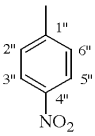
Compound	R	CH_2 (4)	CH_2 (6)	CH_2 (5)	Ar	R	*N*-CH_3
1a		4.65 (ddd) [a] and 3.52-3.59 (m)	4.81 (ddd) [b] and 3.64-3.71 (m)	2.47-2.75 (m)	*3′:* 7.83 (dd) [c] *4′:* 7.40 (ddd) [d] *5′:* 7.61 (dt) [e] *6′:* 8.62 (dd) [e]	*2″and 6″:* 8.32 (d) [f] and 6.96 (d) [f] *3″-5″:* 7.21-7.34 (m)	3.05 (s)
1b		4.63 (ddd) [g] and 3.56-3.62 (m)	4.77 (ddd) [h] and 3.67-3.72 (m)	2.54-2.71 (m)	*3′:* 7.89 (dd) [i] *4′:* 7.46 (ddd) [j] *5′:* 7.67 (dt) [k] *6′:* 8.68 (dd) [k]	*2″ and 6″:* 8.89 (dd) [l] and 7.25 (dd) [l] *3″ and 5″:* 8.13 (dd) [l]	3.07 (s)

[a] J_1=13.3 Hz, J_2=10.3 Hz, J_3=5.1 Hz. [b] J_1=12.3 Hz, J_2=11.3 Hz, J_3=4.6 Hz. [c] J_1=8.2 Hz, J_2= 1.5 Hz. [d] J_1=8.2 Hz, J_2= 7.9 Hz, J_3= 1.5 Hz. [e] J_1= 7.9 Hz, J_2= 1.5 Hz. [f] Broad signal. [g] J_1= 13.8 Hz, J_2= 11.4 Hz, J_3= 5.1 Hz. [h] J_1= 12.9 Hz, J_2= 10.9 Hz, J_3= 4.1 Hz. [i] J_1= 8.1 Hz, J_2= 1.2 Hz. [j] J_1= 8.1 Hz, J_2=7.9 Hz, J_3= 1.2 Hz. [k] J_1= 7.9 Hz, J_2= 1.2 Hz. [l] J_1=9.1 Hz, J_2= 1.6 Hz.

Table II

^{13}C Nmr spectra of 1-(*o*-Nitrophenyl)-2-aryl-3-methyl-1,4,5,6-tetrahydropyrimidinium Salts **1a,b**



Compound	R	C(4)	C(6)	C(5)	C(2)	N-CH_3	Ar	R
1a		49.21	50.99	19.67	162.93	43.46	*1′:* 135.69, *2′:* 144.44, *3′:* 125.80, *4′:* 130.91, *5′:* 135.82, *6′:* 133.07	*1″:* 127.91, *2″:* 125.68, *3″:* 129.39, *4″:* 132.02, *5″:* 129.91, *6″:* 131.06
1b		49.07	50.90	19.12	160.83	43.17	*1′:* 134.53, *2′:* 143.89, *3′:* 125.75, *4′:* 131.22 [a], *5′:* 135.86, *6′:* 133.25	*4″:* 149.32 *1″-3″, 5″-6″:* 133.06, 132.54 [a], 126.98, 124.52, 124.13

[a] Exchangeable assignment.

exist as an enantiomeric pair and their configurational stability at room temperature would be related to the energy barrier between them.

Results and Discussion.

Compounds **1** were synthesized by alkylation of the corresponding 1,2-diaryl-1,4,5,6-tetrahydropyrimidines **2** (Scheme I). ^{1}H and ^{13}C nmr data of salts **1** are shown in Tables I and II respectively. Unequivocal assignment of the ^{1}H and ^{13}C resonances of compound **1a** was made on the basis of its HMQC and HMBC spectra. Assignment of compound **1b** was made on the basis of that of compound **1a**.

Tetrahydropyrimidines **2** show isochronicity of the geminal protons in the trimethylene portion, which appears as two triplets and one pentet in the 300 MHz spectra. In the corresponding quaternary salts (Figure I), instead, such hydrogens show chemical nonequivalence. This spectral pattern would be compatible with the presence of hindered rotation around the Ar-N1 bond, which in turn results in a pair of stable

atropisomers. The presence of a stable stereogenic axis in salts **1** introduces the diastereotopicity of the geminal hydrogens in the trimethylene portion. Conformational chirality in such compounds confirms the preference for the less sterically hindered bisectional rotamers.

In regards to the aryl substituent at position 2 of the heterocyclic ring, it can be observed that in both compounds the two *ortho* positions are chemically nonequivalent. The anisochronicity of such positions could, in principle, be attributed to hindered rotation of the 2-aryl group. However, replacement of an *ortho* hydrogen or carbon atom by another ligand would create an additional stereogenic axis in the molecule and thus the considered atoms are formally diastereotopic even in the absence of hindered rotation of the R-C2 bond.

A computational chemical study of tetrahydropyrimidine **2a**, which does not display atropisomerism at room temperature, indicated that in such compound the amino nitrogen (N1) has substantial sp^3 character [5]. In the corresponding quaternary salt **1a** such nitrogen atom becomes sp^2 as a consequence of electron delocalization in the amidinium system [6]. This would result in shortening of the N1-C2 bond and also in a less staggered conformation for the substituents on N1 and C2. Both changes would intensify interactions between those substituents and would thus raise the energy barrier for the rotation of the Ar-N1 bond, originating configurationally stable atropisomers.

To our knowledge, compounds **1** are the first examples of atropisomeric amidinium salts reported in the literature, and one of the few cases [7] of configurationally stable non-biaryl atropisomers in which a C-N bond is the chiral axis.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were obtained in a Bruker MSL 300 MHz spectrometer using deuteriochloroform as the solvent at a standard concentration of 0.1 *M*. HMQC and HMBC spectra were acquired in a Bruker AVANCE DRX 300 MHz spectrometer. All measurements were performed at a probe temperature of 300 K. Chemical shifts (δ) are reported in parts per million (ppm) downfield from an internal TMS reference. Signals are quoted as s (singlet), d (doublet) dd (double doublet), ddd (double double doublet), t (triplet), dt (double triplet), q (quartet) and m (multiplet). J values are given in Hertz (Hz). Mass spectra (EI) were recorded with a Shimadzu QP-1000 spectrometer operating at 20 eV. Analytical tlc were carried out on aluminium sheets Silica gel 60 F_{254} using chloroform-methanol (9:1) as the solvent. Reagents and solvents were purchased from standard sources and purified according to literature procedures.

Compounds **2a,b** [8] were synthesized by ring closure of the corresponding *N*-(*o*-nitrophenyl)-*N*'-aroyltrimethylenediamines.

1-(*o*-Nitrophenyl)-2-aryl-3-methyl-1,4,5,6-tetrahydropyrimidinium Iodides **1**.

General Procedure.

A mixture of the corresponding 1,4,5,6-tetrahydropyrimidine 2 (5 mmol) and methyl iodide (6 mmol) in anhydrous methylene chloride (50 mL) was refluxed while being protected from moisture. The reaction was monitored by tlc (chloroform:methanol 9:1) until disappearance of the starting material was observed. The solution was evaporated *in vacuo* and the residue purified by recrystallization to yield compounds **1a,b**. The ^{1}H and ^{13}C nmr spectra of these compounds are given in Tables I and II. Yields, physical data and elemental analyses are as follows:

1-(*o*-Nitrophenyl)-2-phenyl-3-methyl-1,4,5,6-tetrahydropyrimidinium Iodide (**1a**).

This compound was obtained in 82% yield, mp 189-190 °C (anhydrous ethanol); ms: m/z 281 (M+.- CH_3I) [9].

Anal. Calcd. for $C_{17}H_{18}IN_3O_2$: C, 48.24; H, 4.29; N, 9.93. Found: C, 48.20; H, 4.26; N, 9.95.

1-(*o*-Nitrophenyl)-2-(*p*-nitrophenyl)-3-methyl-1,4,5,6-tetrahydropyrimidinium Iodide (**1b**).

This compound was obtained in 80% yield, mp 199-200 °C (anhydrous ethanol); ms: m/z 326 (M+.- CH_3I) [9].

Anal. Calcd. for $C_{17}H_{17}IN_4O_4$: C, 43.61; H, 3.66; N, 11.97. Found: C, 43.40; H, 3.71; N, 11.78.

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[*] Author to whom correspondence should be addressed; E-mail: lorelli@ffyb.uba.ar.

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