European Journal of Medicinal Chemistry 45 (2010) 3240–3244

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Laboratory note

Bis-tetrahydroisoquinoline derivatives: Structure analysis of the three stereoisomers of 1,1′-(propane-1,3-diyl)-bis-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline)

Johan Wouters [a,*], Kossay Elasaad [a], Bernadette Norberg [a], Amaury Graulich [b], Jean-François Liégeois [b,**]

[a] Department of Chemistry, University of Namur, rue de Bruxelles, 61, B-5000 Namur, Belgium
[b] Drug Research Center, Laboratory of Medicinal Chemistry, University of Liège, avenue de l'Hôpital, 1 (B36), B-4000 Liège 1, Belgium

ARTICLE INFO

Article history:
Received 19 November 2009
Received in revised form
12 March 2010
Accepted 15 March 2010
Available online 25 March 2010

Keywords:
Tetrahydroisoquinoline
Potassium channel blockers
Absolute configuration
Crystal structure

ABSTRACT

Crystal structure of the three stereoisomers of 1,1′-(propane-1,3-diyl)-bis-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) hydrochloride after resolution by semi-preparative chiral HPLC establishes the absolute configuration and conformation.

1. Introduction

Small conductance Ca^{2+}-activated K^+ (SK) channels play a role in modulating the firing rate and the firing pattern of neurons [1]. A blockade of these targets could be useful for the treatment of cognitive dysfunction, neuronal hyperexcitability or dopamine related disorders [2]. Currently, available blockers are not suitable pharmacological tools being either peptides or quaternized small molecules [2]. Therefore, from *N*-methyl-laudanosine a medium potency blocking compound with a quick reversibility [3], we developed bis-isoquinolinium derivatives with an increased affinity and activity [4]. The permanent charge represents however a serious drawback for brain penetration. Then, the reduction of the isoquinolinium ring led to a series of bis-tetrahydroisoquinolines isolated as a mixture of three stereoisomers with basic property. After resolution by semi-preparative HPLC, we found that one enantiomer of 1,1′-(propane-1,3-diyl)-bis-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) hydrochloride (Fig. 1) showed the highest affinity among a series of analogues while the other enantiomer had the lowest affinity and the meso form had an intermediate one [5]. The basic character is particularly interesting in the context of *in vivo* experiments for assessing the consequence of a blockade of SK channels [6,7]. For further molecular modelling experiments, it is necessary to know the precise configuration of each stereoisomer. The three salts were thus crystallized and the configuration precisely confirmed by X-ray analysis.

2. Results and discussion

2.1. Chemistry

The mixture of stereoisomers was obtained by reduction of the corresponding bis-isoquinolinium analogue [4] with sodium borohydride under nitrogen atmosphere in methanol. Then, each stereoisomer was isolated by resolution of the bis-tetrahydroisoquinoline mixture by semi-preparative chiral HPLC using a Chiralcel® OD-H column and a mixture of 2-propanol (80)/hexane (20) containing 0.05% diethylamine at a flow rate of 1 mL/min (Fig. 2). In these conditions, the retention time for the first eluted enantiomer (E1), the meso and the second enantiomer (E2) are ~7 min, 10 min and 23 min respectively. Finally, the three compounds are converted into their hydrochloride salt which crystallized in a mixture of methanol/diethylether. The hydrochloride forms of both enantiomers E1 and E2 were solubilized in MeOH for specific rotation measurements. The $[\alpha]_D^{20}$ of the first

* Corresponding author. Tel.: +32 81 72 45 50.
** Corresponding author. Tel.: +32 43 66 43 77; fax: +32 43 66 43 62.
E-mail addresses: johan.wouters@fundp.ac.be (J. Wouters), jf.liegeois@ulg.ac.be (J.-F. Liégeois).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.03.020

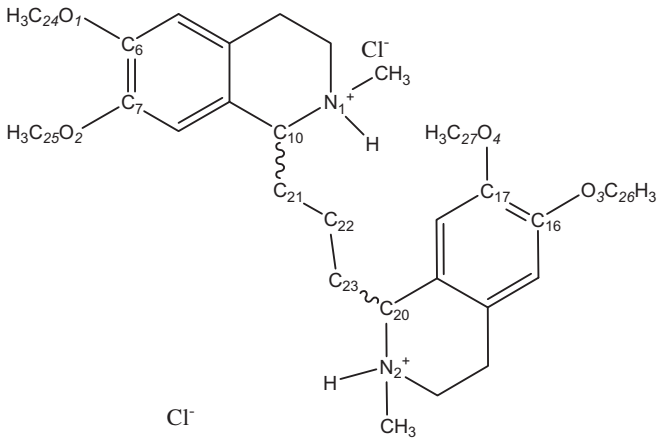

Fig. 1. Chemical structure of 1,1′-(propane-1,3-diyl)-bis-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) dihydrochloride. Numbering of selected atoms is presented.

eluted enantiomer, E1, and the second eluted enantiomer, E2, are +34.8° and −34.5° respectively.

2.2. X-ray studies

For X-ray measurements, crystals of all three stereoisomers of the 1,1′-(propane-1,3-diyl)-bis-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinum) hydrochloride salts were obtained by slow evaporation from an acetonitrile solution. Main crystal data are summarized in Table 1.

The crystal structures of all three stereoisomers, E1, meso, and E2, correspond to the hydrochloride salts of the isoquinoliniums. Interestingly, the meso structure co-crystallized with 5 water molecules.

Stereochemistry of C10 and C20 has been unambiguously established as underlined by the Flack parameters [8] reported in Table 1: C10 (S)/C20 (S) for E1, C10 (R)/C20 (R) for E2, C10 (R)/C20 (S) and C10 (S)/C20 (R) for meso.

Bond lengths and valence angles are similar (within experimental errors) in all three compounds and in agreement with geometries observed in similar structures reported in the literature (e.g. structure of alkaloid (±) carnegine, 1,2-Dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, CSD refocde KORWOD [9]).

In all three structures, the dimethoxy substituents are coplanar to the phenyl ring of the tetrahydroisoquinoline, the methyl groups pointing in opposite directions (see C24–O1–C6–C7, C25–O2–C7–C6, C26–O3–C16–C17, C27–O4–C17–C16, Table 2).

In all three crystal structures, the two 1,2,3,4-tetrahydropyridinium rings adopt a half-chair conformation with theta and phi angles (see puckering parameters, Table 2) close to 60° and $k \times 60°$ [10]. As expected, change of the absolute configuration transforms theta into 180 − theta and phi into 180 + phi [11].

In all three structures, atoms C21 and C23 substitute the chiral center atoms C10 and C20 on the axial position. The methyl groups also occupy the axial position on the protonated nitrogen for all three isomers. The relative position of those methyl groups with respect to the dimethoxy-tetrahydroisoquinolinium rings is however significantly different in the structures of E1 or E2 compared to the meso structure as a consequence of the conformation of the propyl linker (Fig. 3).

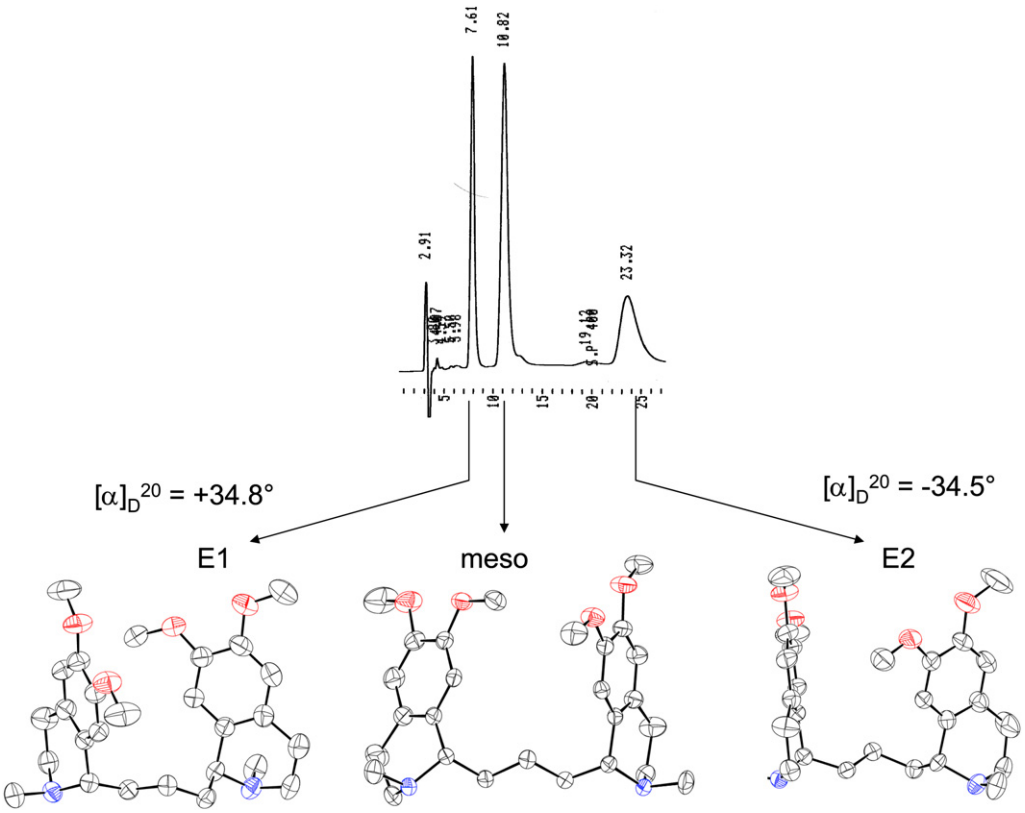

Fig. 2. Resolution of a diastereoisomeric mixture of 1,1′-(propane-1,3-diyl)-bis-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) using a Chiralcel® OD-H column and a mixture of 2-propanol (80)/hexane(20) containing 0.05% diethylamine at a flow rate of 1 mL/min.