Journal of Molecular Structure 936 (2009) 171–176

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

One more chiral drug prone to spontaneous resolution: Binary phase diagram, absolute configuration, and crystal packing of bevantolol hydrochloride

Zemfira A. Bredikhina, Dmitry V. Zakharychev, Aidar T. Gubaidullin, Alexander A. Bredikhin *

A.E. Arbuzov Institute of Organic and Physical Chemistry, Russian Academy of Sciences, Arbuzov St., 8, Kazan 420088, Russian Federation

ARTICLE INFO

Article history:
Received 15 June 2009
Received in revised form 21 July 2009
Accepted 26 July 2009
Available online 3 August 2009

Keywords:
Chiral drugs
Bevantolol
Spontaneous resolution
Conglomerates
Absolute configuration
Crystal packing

ABSTRACT

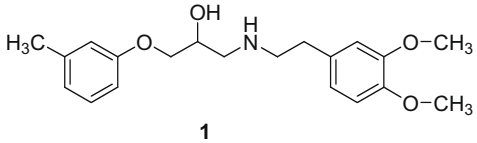
Spontaneous resolution of cardioselective β_1-adrenergic blocker *bevantolol hydrochloride* **1**·HCl was established by IR spectroscopy, differential scanning calorimetry, and by single crystal X-ray analysis both for enantiopure and racemic samples. The absolute configuration of **1**·HCl was evaluated through Flack parameter method. The molecular structure and crystal packing details were evaluated; the symmetry independent fragment of the *P*1 unit cell consists of two molecules which have almost identical spatial arrangement, but differ sufficiently in the nature of nitrogen atoms: quaternary form in one case and free amine form in the other.

1. Introduction

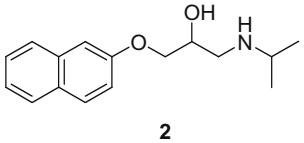
It's a well established fact that in the family of β-adrenergic blockers with a general formula of $ArOCH_2CH(OH)CH_2NHAlk$, the (*S*)-enantiomers are eutomer components of the racemic drug, whereas (*R*)-enantiomers (distomers) usually display other (often undesirable) activity [1]. Among a plethora of ways leading to enantiopure β-blockers (as well as to any other enantiopure target organic substances), the direct resolution approaches based on the phenomenon of spontaneous resolution upon crystallization are of special interest because they need no resolving agents and/or any other chiral auxiliaries for realization [2,3]. Spontaneous resolution presumes conglomerate, i.e., a mechanical mixture of enantiopure single crystals formation during the melt or solution crystallization of a racemic substrate.

Some years ago Neau, Shinwari, and Hellmuth reported the thermal analysis results on the conglomerate forming nature for two β-blocker hydrochlorides, namely bevantolol (**1**) and propranolol (**2**) [4].

Checking their thermochemical results for propranolol **2**, we have recently confirmed that the free base of **2** forms a stable racemic compound, and the eutectic was found in the close vicinity of a pure enantiomer [5]. However, in contrast to the findings of Neau



1



2

* Corresponding author. Tel.: +7 843 273 45 73; fax: +7 843 273 18 72.
E-mail address: baa@iopc.knc.ru (A.A. Bredikhin).

0022-2860/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.molstruc.2009.07.032

et al., the phase diagram of propranolol hydrochloride shows no eutectic but a shallow plateau at the racemic composition. Therefore, despite low stability of its racemic compound **2**·HCl is *not capable* of the conglomerate formation, even if its racemic compound is very unstable [5]. The reasons for this instability were disclosed in our subsequent crystallographic investigation of propranolol hydrohalogenides [6]. It turns out that **2**·HCl (as well as **2**·HBr) belongs to a rare class of racemic compounds crystallizing in a "chiral" space group $P2_1$ having two enantiomers as two symmetry independent molecules in the crystal unit cell. The enlargement of the anion in the case of **2**·HI breaks this borderline situation and both enantiomers became symmetry constrained fragments in the "achiral" centrosymmetric $P-1$ unit cell, which results in the formation a rather stable racemic compound. On the contrary, diminution of the anion in the case of **2**·HF leads to the formation of a common racemic conglomerate crystallizing in the same $P2_1$ space group as for **2**·HCl, but now having only one symmetry independent molecule, (*R*)-**2** or (*S*)-**2**, in the crystal unit cell [6].

Having these results in hand, we then decided to scrutinize crystallization nature of the other mentioned in Neau et al. paper drug bevantolol using infrared spectroscopy (IR), differential scanning calorimetry (DSC), and single crystal X-ray diffraction analysis.

Bevantolol, or 1-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-3-(3-methylphenoxy)-2-propanol (**1**), is a popular cardioselective β_1-adrenergic blocker prescribed in the form of a hydrochloride as an antianginal, antihypertensive and antiarrhythmic remedy for various heart disorders [7]. The configuration of the **1**·HCl enantiomers has been established by the chemical correlation method following the next reaction succession [8] (Scheme 1):

Although the aforementioned configuration attribution can be considered as quite reliable, the presence of the first step in the reaction sequence where the complete configuration inversion was postulated leaves a chance for mistake. Taking into account the importance of the substrate, it is desirable to use direct X-ray methods for establishing the absolute configuration, which was another goal of our work. To the best of our knowledge, the crystal structure for bevantolol has not yet been reported neither for racemic nor for scalemic samples, which is in itself an obstacle to understanding its properties from both theoretical and practical point of view.

2. Experimental

Optical rotations were measured on a Perkin-Elmer model 341 polarimeter (everywhere over the paper the value of specific rotation is given in deg mL g^{-1} dm^{-1}, and the concentration of solutions *c* appears in g/100 mL). Melting characteristics were measured on a Perkin-Elmer Diamond DSC differential scanning calorimeter in aluminum pans with the rate of heating of 10 °C min^{-1}. The mass of the samples amounted to approximately 2.5 mg. HPLC analyses were performed on a Shimadzu LC-20AD system controller, and UV monitor 275 nm was used as a detector. The column used, from Daicel, Inc., was Chiralcel OD (0.46 × 25 cm); column temperature 40 °C; eluent hexane:isopropanol:Et_2NH = 60:40:0.1; flow rate 0.4 mL/min.

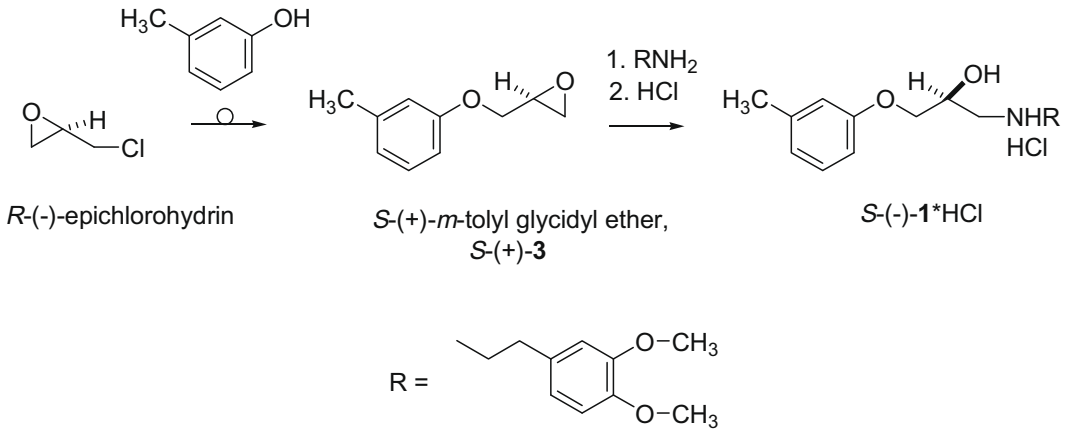
2.1. Synthesis

2.1.1. General

Racemic epichlorohydrin, 3,4-dimethoxyphenethylamine and *m*-cresol were commercially available. (*S*)-Epichlorohydrin was prepared by Jacobsen kinetic hydrolytic resolution of *rac*-epichlorohydrin [9]. Racemic and scalemic **1**·HCl samples were synthesized by analogy with a published procedure [10] from racemic and scalemic glycidyl *m*-tolyl ether **3** and 3,4-dimethoxyphenethylamine; in so doing (*R*)-(+)-**1**·HCl was obtained from (*R*)-(−)-**3** and (*S*)-(−)-**1**·HCl was obtained from (*S*)-(+)-**3** correspondingly. In turn (*R*)-(−)-**3** was obtained from (*S*)-(+)-epichlorohydrin and *m*-cresol. The sample of (*S*)-(+)-**3** was obtained by us earlier through Jacobsen like kinetic resolution of *rac*-**3** [11]. An example of the target compound synthesis is given below.

2.1.2. (R)-1-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-3-(3-methylphenoxy)-2-propanol hydrochloride, (R)-bevantolol hydrochloride, (R)-1·HCl

(*R*)-1,2-Epoxy-3-(3-methylphenoxy)-propane, (*R*)-**3**, {$[\alpha]_D^{20}$ = −11.8 (*c* 1.7, MeOH)} (2.26 g, 13.7 mmol) and 2.48 g (13.7 mmol) of 3,4-dimethoxyphenethylamine in 5 mL of ethanol were stirred at 25–30 °C for 24 h. The reaction was monitored by TLC. After disappearance of the starting epoxide the mixture was evaporated to dryness and the residue was dissolved in EtOAc and gaseous HCl was passed through the resulting solution to give 3.1 g (60%) of (*R*)-**1**·HCl. Mp 155–157 °C (CH_3CN/EtOH); $[\alpha]_D^{20}$ + 17.9 (*c* 1.1, EtOH); $[\alpha]_D^{20}$ + 18.3 (*c* 0.95, MeOH) 99.9% ee (HPLC; t_R = 8.4 min). [Cf. lit.[8] for (*S*)-enantiomer mp 151–153 °C; $[\alpha]_D^{23}$ − 16.7 (*c* 0.82, MeOH), 98% ee]. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.26 (s, 3H, CH_3), 3.22–3.28 (m, 6H, $CH_2N^+CH_2CH_2$), 3.82 (s, 6H, OCH_3), 3.97 (dd, ^2J = 9.8, ^3J = 5.7 Hz; 1H, $1OCH_2$), 4.05 (dd, ^2J = 9.8, ^3J = 4.4 Hz; 1H, $1OCH_2$), 4.68 (m, 1H, OCH), 5.33 (broad s, OH); 6.61–6.64 (m, 2H, Ar), 6.72–6.77 (m, 4H, Ar), 7.09 (t, *J* = 7.6, Hz, 1H, Ar); 8.92 (broad s, N^+H), 9.80 (broad s, 1H, N^+H). (Cf. lit.[8] for ^{1}H NMR 400 MHz).



Scheme 1.