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Conglomerate formative precursor of chiral drug timolol: 3-(4-Morpholino-1,2,5-thiadiazol-3-yloxy)-propane-1,2-diol

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

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

HIGHLIGHTS

- Crystallization features of chiral drug timolol precursor are investigated.
- 3-(4-N-morpholino-1,2,5-thiadiazol-3-yloxy)-propane-1,2-diol is a conglomerate formative compound.
- Hydrogen O–H···O′H bonds are responsible for dense character of homochiral crystal packing.
- Near-ideal phase behavior of the studied diol create the preconditions for its obtaining in an enantiopure form.

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ABSTRACT

Solid state properties of 3-(4-N-morpholino-1,2,5-thiadiazol-3-yloxy)-propane-1,2-diol **3**, the synthetic precursor of popular drug timolol, have been investigated. The original solubility test, the data of X-ray diffraction and DSC methods indicate that the compound is prone to spontaneous resolution. Diol **3** crystallizing from both enantiopure or racemic feed material forms "guaifenesin-like" crystal packing in which the classic H-bonded bilayers, framed in both sides by hydrophobic molecular fragments, act as the basic supramolecular motif. The main chain conformation of the molecules in the crystals of diol **3** differs from that in the guaifenesin crystals, and this fact changes the absolute configuration of spiral columns formed by intermolecular hydrogen bonds in crystals of **3** as compared with guaifenesin crystals.

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Introduction

Chirality is a fundamental property of an object to be non-superposable with its mirror image. This property manifests itself in the whole scale of natural objects, from elementary particles to the Universe [1]. Only one of these manifestations, but perhaps the most important for a human being, is the homochirality of terrestrial life. Once in the chiral environment of a living organism, different enantiomers (stereoisomers related to the mirror symmetry, but not coincident with each other) act differently showing different pharmacological, toxic, pharmacodynamic and pharmacokinetic properties [2,3]. This fact is largely responsible for the growing demand for enantiopure substances and materials.

For instance, (*S*)-1-[(1,1-dimethylethyl)-amino]-3-[[4-(morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol, unselective β-adrenoblocking agent timolol **1** (Scheme 1), is an example of a chiral drug, widely used as an anti-hypertensive and anti-glaucoma remedy under a variety of trade names in the form of single S-enantiomer [4,5].

Alongside with the chemical purity, the enantiomeric purity is a very important characteristic for single enantiomeric drugs. For a chemical purification and enantiomeric enrichment of crystalline compounds, to which the timolol belongs, a crystallization from a suitable solvent is the most commonly used approach. Since the time of the classic H.W.B. Roozeboom publication [6] it is known that for a solid chiral substance sample of an intermediate enantiomeric composition, $0 < ee < 1$, the course and the results of crystallization are governed by the type of its phase diagram [7,8]. Typical cases of this phase behavior are illustrated in Fig. 1.

In nature, the most frequent case is the case of normal racemic compound, when in the solid phase enantiomers form a molecular addition compound of 1:1, and the phase diagram is characterized by two eutectics symmetrically arranged on both sides of the

* Corresponding author. Tel.: +7 843 272 73 93; fax: +7 843 273 18 72.
E-mail address: baa@iopc.ru (A.A. Bredikhin).

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racemic compound (Fig. 1a). In this case, during the crystallization of a saturated solution of the sample with enantiomeric excess *ee* higher than enantiomeric excess of the eutectic, $ee > ee_{eu}$, the solid phase becomes enriched with the prevailing enantiomer.

The cases of pseudoracemates are rare in occurrence than the other two. They represent the solid solution of enantiomers and hence they have no eutectic on the phase diagram (Fig. 1c). In this case, a significant enantiomeric enrichment by crystallization is problematic, if not impossible. Recently, we have found that timolol maleate belongs to this namely type [9].

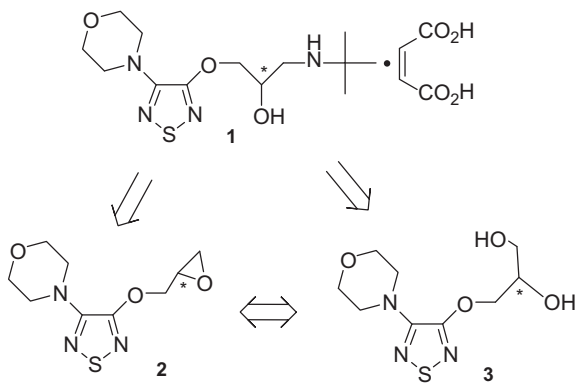
The most favorable for producing chiral substance in the non-racemic form (and/or for further enantiomeric enrichment of the sample to any desired level) is the case of conglomerate, when there is only one eutectic on the phase diagram (Fig. 1b). As can be seen from the figure, the racemic conglomerate itself is a mechanical mixture of enantiopure crystals, thus the stereoselective crystallization takes place in this case, and the substance undergoes spontaneous resolution. Stereoselective crystallization is becoming more and more attractive as a method for obtaining non-racemic substances thanks to freedom from any of chiral auxiliary additives and catalysts, or enantioselective chromatographic phases [8]. The spontaneous resolution phenomenon and direct separation techniques and their limitations are subject of permanent interest and well described in the review works [7,10,11].

Several synthetic approaches to timolol **1** are described in the literature. The most often mentioned synthetic precursors in the processes are 4-[4-(oxiran-2-ylmethoxy)-1,2,5-thiadiazol-3-yl]-morpholine **2** and 3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)-propane-1,2-diol, **3** (Scheme 1). It may be noted that the epoxide **2** and diol **3** can be chemically transformed into each other. Recently, we have shown that epoxide **2** is prone to spontaneous resolution, but its behavior is complicated by the presence of the areas of partial mutual solubility of enantiomers on the phase diagram [12]. As far as we know, for diol **3** the data concerning the type of chirality driven crystallization, as well as its solubility and crystal structure have not been known. In this paper we attempt to fill this gap.

Experimental

Instrumentation

Optical rotations were measured on a Perkin-Elmer model 341 polarimeter (concentration *c* is given as g/100 ml). Melting points for general purposes were determined using a Boëtius apparatus and are uncorrected. Enantiomeric purity was checked by HPLC analysis performed on a Shimadzu LC-20AD system controller. The mass of the samples for solubility determination and calorimetry was controlled with a Sartorius CPA2P microbalance; the measurement resolution is 1 μg.



Scheme 1. Chiral drug timolol **1** and its synthetic precursors epoxide **2** and diol **3**.

Differential scanning calorimetry (DSC) served as a working method for thermal measurements and for construction of a binary fusion phase diagrams in the present work. The melting curves 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 ~1 mg. Temperature scale and heat flux were calibrated against the data for indium and naphthalene.

Materials

The samples of *rac*-**3** and (*R*)-**3** required for investigations were obtained according to [13], and further were purified by column chromatography.

rac-3-(4-Morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propane-1,2-diol, rac-3

White or beige solid; mp 97–98 °C (EtOAc/hexane = 3:2). Lit. [14]: mp 95–96 °C; lit. [13]: mp 89–91 °C.

(R)-3-(4-Morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propane-1,2-diol, (R)-3

White needles; mp 120–121 °C (EtOAc/hexane = 3:2); $[\alpha]_D^{20} = -17.5$ (*c* 1, EtOH); 99.9% *ee* [chiral HPLC analysis; Daicel Chiralcel OJ (0.46 × 25 cm) column; column temperature 20 °C; eluent: hexane/2-propanol = 8:2); flow rate: 1.0 mL/min; UV detector 298 nm; t_R = 15.2 min (minor), t_R = 17.8 min (major)]. Lit. [13] (for *S*-enantiomer): mp 118–120 °C, $[\alpha]_D^{20} = +18.2$ (*c* 0.9, 95% EtOH).

Solubility measurements

Filters Millipore 0.45 μm PTFE hydrophilic were used for the samples filtering. Micro syringes Hamilton (precision within ±1%) were used for analytical sampling and for adding fixed volumes of solvent. The mass of the samples was controlled with Sartorius CPA2P balance (accuracy ±1 μg). The solvents used were methylene chloride and toluene. All measurements were carried out at a temperature of 20 ± 0.2 °C.

The solubility of racemic and enantiopure samples was determined by chromatographic control of the concentration of saturated solution, equilibrious with the corresponding crystalline phase. For this purpose to pure solvent (~3 mL) the corresponding solid phase was sequentially added by weighted portions with stirring until a stable turbidity of the liquid and the sediment at the bottom were observed. The total amount of the added substance was 20 mg of enantiopure **3** and 50 mg of racemate for measurements in methylene chloride and 3 mg of enantiopure **3** and 6 mg of racemate for measurements in toluene. The vial was hermetically sealed by stopper and the slurry was stirred at a constant temperature (20 ± 0.2 °C) during the day; the continual presence of the large excess of solid phase was monitored visually. After stopping the stirring and sedimentation, the liquid phase was sampled by syringe and filtered. The samples of equilibrium solution of **3** in toluene were subjected to chromatographic analysis directly. In the other experiments, an aliquot of the methylene chloride solution (0.5 mL) was filtered, evaporated to dryness in vacuo, the residue was dissolved in 5 mL of isopropyl alcohol, and the resulting solution was analyzed chromatographically.

All experiments were repeated twice, and three chromatographic measurements were performed for each system. The absolute values of the solubility in methylene chloride totaled

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