Tetrahedron: *Asymmetry* xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

The effective direct resolution procedure for the chiral drug bevantolol hydrochloride

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ARTICLE INFO

Article history:
Received 11 March 2016
Accepted 23 March 2016
Available online xxxx

ABSTRACT

The solubility of the chiral drug *bevantolol hydrochloride* **1** in water and the azeotropic mixture ethanol–water has been investigated. It was found that *rac*-**1** meets the requirements of Meyerhoffer's rule, so it was possible to reduce the ternary diagram, describing the solubility of **1**, to a pseudo binary form, which facilitates the analysis of crystallization processes caused by temperature changes. On this basis, the effective and robust resolution procedure of racemic bevantolol hydrochloride by a preferential crystallization approach has been realized successfully.

1. Introduction

The scale of' fundamental problems associated with the phenomenon of spontaneous resolution of enantiomers during crystallization is recognized by the scientific community as 'one of the true challenges for science in the 21st century'.[1] No less remarkable is the practical aspect of this phenomenon. Spontaneous resolution makes it possible to obtain pure enantiomers, the importance of which is increasing day by day, by direct methods, which do not require the use of enantiopure auxiliary substances and/or materials.[2,3]

The oldest of the direct methods is the preferential crystallization. Described in 1866,[4] it started to become more common in chemical practice in the second half of the twentieth century[5,2] and currently has a solid theoretical background and a variety of embodiments.[6] Another modification of the direct resolution, relatively recently taken its shape, represents the so-called attrition-enhanced deracemization,[7] aka 'Viedma ripening'.[8] This approach is based on the different rates of the dissolution of crystals of different sizes (Ostwald ripening[9]), and can be applied to the deracemization of only those substrates that combine the ability for spontaneous resolution with the ability to take part in (spontaneous or induced) racemization in solution. The obvious limitations of this approach are compensated, firstly, through the ability to transform all of the available racemate into a single enantiomer. Secondly, this modification allows the resolution to proceed as a continuous process, as opposed to batch-crystallization for the majority of preferential crystallization variants.

Currently, direct methods for racemate resolution are deeply understood from a fundamental and engineering point of view. We believe that their penetration into routine practice would be facilitated through the widening of the essential non-racemic compounds prone to spontaneous resolution in racemic form. It appears that the registered chiral active pharmaceutical ingredients could be the objects of choice in this regard.

The literature has many examples of how direct methods are used for the deracemization of substances, which are used as synthetic precursors for single enantiomeric active pharmaceutical ingredients. For example, the resolution of racemic *threo*-1-(4-nitrophenyl)-2-aminopropane-1,3-diol, the (*R*,*R*)-enantiomer of which is used in the production of chloramphenicol.[10,11] Racemic modafinic acid, a key intermediate in the synthesis of (*R*)-modafinil, was resolved in a preparative scale using a preferential crystallization approach.[12] The direct resolution of *rac*-2-(benzylideneamino)-2-(2-chlorophenyl)acetamide underlies the synthesis of (*S*)-clopidogrel.[13,14] Among recent publications we refer to our synthesis of mexiletine enantiomers based on the preferential crystallization of *rac*-(2,6-dimethylphenoxy)propane-1,2-diol.[15]

Another frequently used option that takes advantage of the enantioselective crystallization in the synthesis of nonracemic active pharmaceutical ingredients, is the conversion of a racemic target product, incapable of spontaneous resolution, in a simple derivative, which crystallizes in the form of normal conglomerate. By this strategy, among the hundreds of *fenfluramine* and *norfenfluramine* racemic salts, which have been studied, eight salts crystallized in the form of a conglomerate were found, and six of those were resolved into enantiomers via preferential crystallization.[16] Pure enantiomers of atenolol were obtained via preferential crystallization in the form of salts with *p*-toluic acid.[17] Racemic

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http://dx.doi.org/10.1016/j.tetasy.2016.03.012
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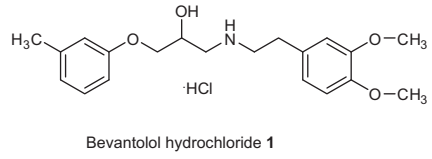
propranolol hydrochloride crystallizes to form a normal racemic compound,[18] whereas its hydrofluoride becomes a conglomerate and can be resolved into its enantiomers via resolution by entrainment.[19] Medetomidine is used in medical practice as a hydrochloride, but becomes a conglomerate in the form of oxalic acid salt.[20] The registered racemic forms of omeprazole (free acid and its magnesium salt) are not prone to spontaneous resolution. At the same time the omeprazole potassium salt solvates with two molecules of ethanol and can be separated into individual enantiomers by direct methods in a batch crystallization mode,[21] and in a continuous mode.[22]

The most spectacular from the standpoint of demonstrating the feasibility of the spontaneous resolution are the direct resolution of chiral racemic active pharmaceutical ingredients. Apparently, methyldopa should be considered as the first example of this kind, because the pure (*S*)-enantiomer of it has been produced industrially via the direct resolution of the racemic product.[11] Spontaneous resolution is a property exhibited by albuterol sulfate[23] and calcium pantothenate.[24] In our previous publications we have shown that the ability for spontaneous resolution is inherent in active pharmaceutical ingredients guaifenesin,[25,26] mephenesin[27] and methocarbamol.[28]

Potentially, this short list can be expanded by including the active pharmaceutical ingredient bevantolol, the hydrochloride of which is used in medical practice, and is crystallized in the form of a normal conglomerate.[29,30] Herein we examine the possibility of using a direct resolution approach for to obtain the pure enantiomers of bevantolol.

Bevantolol, chemical name 1-[[2-(3,4-dimethoxyphenyl)ethyl] amino]-3-(3-methylphenoxy)-2-propanol, is a popular cardiovascular remedy. It is used in the treatment in the form of hydrochloride **1** (see Scheme 1) under the trade names Ranestol, Sentiloc, Vantol.[31]



Bevantolol hydrochloride **1**

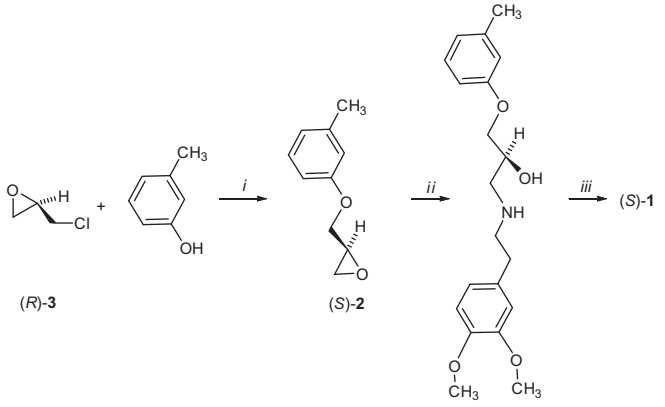
Scheme 1. Chemical structure of bevantolol hydrochloride **1**.

Bevantolol is a β_1-adrenoceptor antagonist that has been shown to be as effective as other beta blockers for the treatment of angina pectoris and hypertension. Experiments confirm both agonist and antagonist effects on α-receptors, in addition to antagonist activity at β_1-receptors.[32,33] For the family of β-adrenergic blockers with general formula $ArOCH_2CH(OH)CH_2NHAlk$, it has been shown that the (*S*)-enantiomers are eutomer components of the racemic drug, whereas the (*R*)-enantiomers (distomers) usually display other (often undesirable) activities.[34] Racemic bevantolol as well as its enantiomers also possesses different biological activity. Thus (*S*)-(−)-bevantolol is a stereoselective β_{1L}-AR_S^2 antagonist; this substance, unlike its (+)-enantiomer, attenuates the increase in heart rate caused by (±)-CGP 12177,[35] whereas *rac*-**1** only tended to decrease the positive chronotropic effect of (±)-CGP 12177 and is not considered to be an antagonist of β_{1L}-adrenoceptors.[36]

The main advantages of homochiral (single enantiomer, enantiopure) substances include reduced dosage and reducing the side effects associated with off-target biological activity of the distomer (undesired enantiomer). The latter property makes it possible to create new single enantiomer drugs with different indications on the basis of a racemate. Due to a general trend towards replacing the racemic drugs with their enantiopure analogues,[37] it is useful to have a convenient approach to the individual enantiomers of bevantolol.

2. Results and discussion

For the synthesis of racemic bevantolol hydrochloride, the reaction of 3,4-dimethoxyphenylethylamine with racemic 1-chloro-3-*meta*-tolyloxy-2-propanol or 2-*meta*-tolyloxymethyloxirane *rac*-**2** has been used.[38,30] Racemic oxirane *rac*-**2** was obtained from racemic epichlorohydrin *rac*-**3** and *meta*-cresol. Enantiomeric (*R*)-**2** and (*S*)-**2** were prepared analogously from (*S*)-**3** and (*R*)-**3**, respectively. For the synthesis of enantiomeric bevantolol samples, needed as seeds in the initial resolution step, we reacted 3,4-dimethoxyphenylethylamine with enantiopure oxiranes (*S*)-**2** or (*R*)-**2**. The general sequence of the reaction is illustrated in Scheme 2 with the (*S*)-enantiomer of bevantolol.



Scheme 2. Reagents and conditions: (i) 2 M aq NaOH, 60 °C, 2 h; (ii) 3,4-dimethoxyphenylethylamine, EtOH, rt; (iii) gaseous HCl, EtOAc.

As noted above, the tendency for the crystallization of racemic **1** as a racemic conglomerate has already been proved.[30] However, this very feature is a necessary but not sufficient condition for the successful implementation of the preparative methods of direct resolution. It is known that about half of conglomerate formative compounds demonstrate poor efficiency in the stereoselective crystallization processes.[39–41] In addition, for efficient separation some enantiomeric pre-enrichment of the initial mixture is often required.[25] Currently, there are no tests except for an experiment to assess the ability of a substance to undergo preparative spontaneous resolution.

The choice of solvent is of great importance in the development of methods of direct resolution. It should not have a too high or not too low dissolving power with respect to the resolvable substrate. An important characteristic of the solvent is the gap $\Delta T = T_H - T_N$, where the separating T_H, the temperature at which the original undersaturated solution becomes saturated, and T_N, temperature at which spontaneous crystallization becomes noticeable without external seeds.[42] Finally, the solvent of choice should be environmentally friendly, accessible and inexpensive as possible. It is known that compound **1** is very soluble in methanol, chloroform and DMSO, but in the light of these requirements, none of these solvents look attractive. It is also known that compound **1** is soluble in water, but the quantitative data available differ by orders of magnitude and cannot be regarded as reliable. For this reason, we have carried out preliminary measurements of the solubility of the racemic bevantolol hydrochloride in several available solvents. The data are presented in Figure 1.

Figure 1 shows that ethyl acetate is not suitable practically for crystallization, since even at 73 °C the concentration of the saturated solution is only C_{sat} = 1.4 mg/ml. Using isopropanol (C_{sat} = 6.4 mg/ml; 45 °C) or acetonitrile (C_{sat} = 8.3 mg/ml; 41 °C) requires working with dilute solutions. Ethanol (C_{sat} = 60.0 mg/ml; 43 °C) represents a suitable solvent for the resolution of

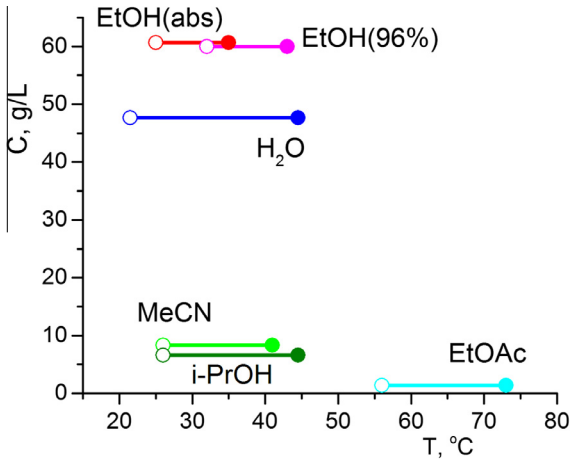


Figure 1. Solubility of *rac*-**1** in various solvents; filled circles correspond to T_H values and contour circles correspond to T_N values.

rac-**1**, however the value of $\Delta T = T_H - T_N$ is sufficiently small and it is approximately 10–11 °C. The solubility of *rac*-**1** in water is somewhat lesser (C_{sat} = 47.7 mg/ml; 44.5 °C), but the value ΔT is 20 °C. Both of these solvents have been tested by us in the process of resolution of *rac*-**1** by entrainment. Since absolute ethanol is hygroscopic, we had to deal with an azeotrope mixture ethanol–water; the measured solubility characteristics for this solvent consisted of C_{sat} = 60.7 mg/ml at 35 °C; $\Delta T \approx 10$ °C.

In deciding on the stereoselective crystallization process parameters, it is desirable to know the solubility phase diagram for the system 'solvent–enantiomers', built with due regard for the metastability zone of the supersaturated solution of the crystalline phase in the solvent.[6,42] It should be noted that the construction of a total phase diagram of the ternary system (two enantiomers and a solvent) requires a large amount of experimental data. Furthermore, a ternary solubility diagram is usually represented as an isothermal cut, and it is inconvenient to represent the crystallization process caused by changing (lowering in our case) the temperature. As shown below, in some cases the information contained in the ternary phase diagram can be adequately represented in the binary diagram, which takes account of the temperature.

Figure 2 shows the temperature dependence of the solubility of individual bevantolol hydrochloride stereoisomers in ethanol and water. Olive solid circles denote the experimental results in terms of dissolution, and olive contour circles denote the starting points of crystallization for enantiopure samples. Similarly, the behavior of *rac*-**1** in a cycle of 'dissolution-crystallization' is characterized by a magenta color. Concentration values for the racemate are given in terms of the individual stereoisomer (i.e., the real values of the concentration of the racemate are halved).

Analysis of the charts suggests that for both studied systems, the experimental points, which correspond to dissolution process, both for enantiopure and for racemate samples fall well on a single curve (solid lines). This means that these systems well meet the requirements of Meyerhoffer's rule (the racemate solubility equals twice the enantiomer solubility),[43] i.e., their behavior is consistent with the behavior of a normal conglomerate and not complicated by concentration and solvation effects.

The experimental points that correspond to the crystallization (contour circles in olive and magenta for enantiopure and racemic samples, respectively) show a tendency to decrease the interval ΔT in passing from nonracemic to racemic samples. However, taking into account the stochastic nature of the lower boundary of the metastable zone, a considerable variance of the data set appears natural, and the bottom boundaries of metastable supersaturated solutions are satisfactorily described by the averaged dashed curves. All of this gives us hope that when describing the dissolution and crystallization processes in the studied systems, the mutual influence of bevantolol enantiomers in solution can be neglected. In turn, this allows the use of the pseudo binary phase diagram 'enantiomer–solvent' to describe the phase behavior of the systems under consideration and when choosing a stereoselective crystallization conditions.

Figures 3 and 4 show the pseudo binary phase diagrams 'bevantolol hydrochloride–ethanol' and 'bevantolol hydrochloride–water'. Figures (a) represent in diagram form their general theoretical view. Figures (b) show the experimentally investigated areas; these fragments are similar to Figure 2a and b and retain the notation adopted there.

Figures 3c and 4c are of particular interest to the task solution of *rac*-**1** direct resolution into individual enantiomers. They represent a detailed view of the region of the phase diagram near the temperature interval 20–40 °C, i.e., near the ambient temperature. Using moderate temperatures during the resolution simplifies a system thermostating and supersaturated solution sampling for process control, as well as allows minimizing the problems associated with solvent evaporation.

The graphs indicate that in this area both the absolute value of the solubility of compound **1** and the metastable zone width in both solvents are satisfactory for the stereoselective crystallization of bevantolol enantiomers. Preliminary experiments demonstrated that when using ethanol, the crystallization rate decreased rapidly with decreasing solution supersaturation, so the process was

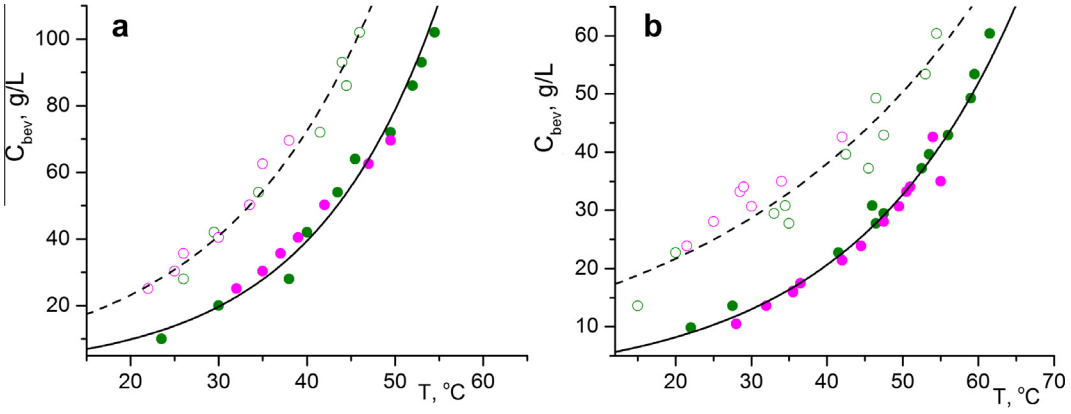


Figure 2. Temperature dependence of the solubility (solid lines) and the reverse process of crystallization (dotted lines) of *rac*-**1** (magenta) and (*S*)-**1** (olive) in rectified ethanol (a) and in water (b).

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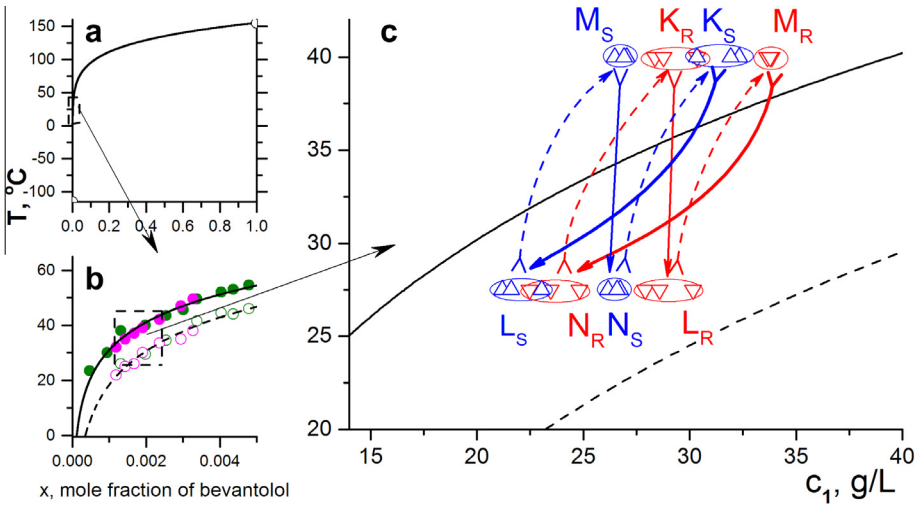

Figure 3. (a) General view of the solubility phase diagram for the system 'ethanol–bevantolol hydrochloride'; the dotted rectangle designated area which is enlarged in chart b. (b) Experimentally studied region of the phase diagram; designations are the same as those adopted in Figure 2. The dotted box denotes the region, represented enlarged in figure c. (c) Trajectory of the cyclic process of preferential crystallization of the individual enantiomers on the pseudo binary phase diagram (explanations are in the text).

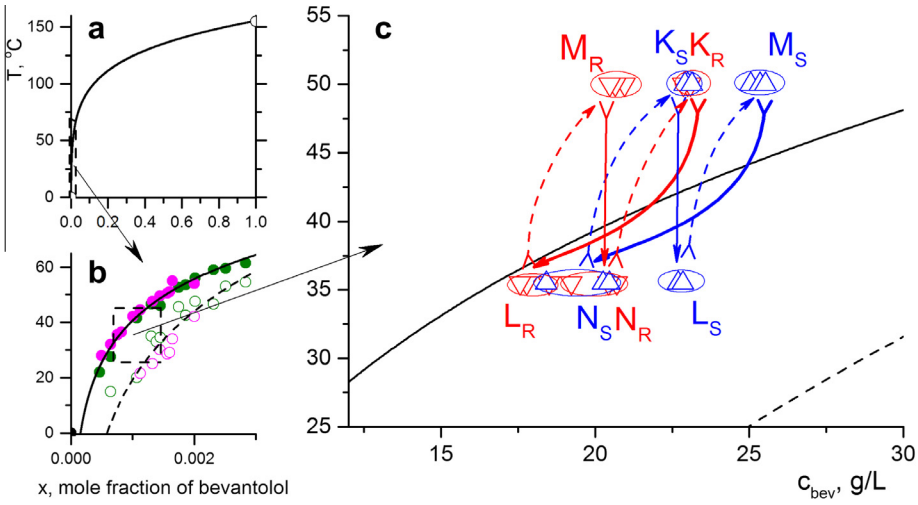

Figure 4. Solubility phase diagram for the system 'water–bevantolol hydrochloride'. Designations are the same as in Figure 3.

preferably carried out near the bottom temperature boundary of the metastable zone. In aqueous solution, the crystallization proceeds efficiently to almost complete exhaustion of supersaturation of the crystallizing component. At the same time, the bottom boundary of the metastable zone for this system shows a high degree of stochasticity, indicating that the process should be conducted near the upper boundary of the metastable zone where the system has much higher stability. The following process conditions were chosen based on these considerations: crystallization temperature—no more than 28 °C for ethanol and no more than 36 °C for water; the initial concentration of the racemate was ~60 mg/ml in ethanol and ~40 mg/ml in water.

In Figures 3c and 4c, the concentrations of each component before and after a regular resolution step (nodal points) are designated by triangles in red for (*R*)-**1**, and by inverted blue triangles for (*S*)-**1**. Similar points for different cycles are grouped and enclosed by ovals of an appropriate color; the ovals are designated by capital letters. Red and blue arrows (trajectories) schematically represent the change in concentration of corresponding enantiomer during the realization of resolution by entrainment. Let us discuss the details of the process by the example of the direct resolution of compound **1** in ethanol, Figure 3c.

The crystallization process starts from a point in the K_S zone, which corresponds to the solution of the racemic composition at a temperature above the boundary of the saturated solution (solid black line in the phase diagram). Cooling this solution to a temperature just below this boundary (~27 °C) with seeding with the (*S*)-enantiomer gives a precipitate which consists substantially of this enantiomer. At that its concentration in solution decreases (heavy blue line K_SL_S). At the same time, the second enantiomer remains in a supersaturated solution, and its concentration does not significantly change (thin red line K_RL_R). After finishing this step, the precipitated (*S*)-enantiomer is separated from solution. The solution is then heated above the saturation temperature, and the replenishing portion of the racemate is introduced, resulting in an increase in the concentration of each enantiomer. This stage of the cycle in the phase diagram is designated by dashed lines L_SM_S and L_RM_R. Upon cooling to supersaturation followed by seeding with the (*R*)-enantiomer, this namely isomer precipitates (heavy red line M_RN_R). The concentration of the (*S*)-enantiomer remains fairly constant (thin red line M_SN_S). After heating and adding an appropriate amount of the racemate, the cycle is closed, and the system returns to virtually the initial composition (dotted lines N_SK_S and N_RK_R).

Table 1
Resolution by entrainment of *rac*-bevantolol hydrochloride in ethanol (96%) (100 ml, 10 mg of crystal seeds on every run, crystallization temperature 27.5 ± 0.5 °C)

Run	Added amount of *rac*-**1**, g	Operation amount of enantiomers, g		Resolution time, min	(*R*)-**1** and (*S*)-**1** obtained				
					Yield, g	*ee*[a], %	*YE*[b]		*DR*[c], %
		(*R*)-**1**	(*S*)-**1**				g	%	
1	6.070	3.035	3.035	120	(*S*) 0.750	94.9	0.702	23.1	54.6
2	0.740	3.386	2.684	130	(*R*) 1.170	94.7	1.098	32.4	85.5
3	1.160	2.837	3.233	140	(*S*) 1.160	92.1	1.059	32.8	82.4
4	1.150	3.366	2.704	140	(*R*) 1.050	94.2	0.980	29.1	76.3
5	1.040	2.877	3.193	150	(*S*) 1.050	96.4	1.002	31.4	78.0
6	1.040	3.378	2.692	160	(*R*) 1.010	92.9	0.928	27.5	72.2

[a] *ee*: enantiomeric excess (HPLC).
[b] *YE*: Yield enantiomer; *YE*(g) = [Yield(g) × *ee* (%)]/100 − 0.010; *YE* (%) = [*YE*(g) × 100]/operation amount of (*R*)- or (*S*)-**1**(g).
[c] *DR*: degree of resolution; *DR* (%) = YE(g) · 100/[0.5 · (6.07–3.5)]; 3.5—solubility *rac*-**1** in 100 ml EtOH (96%) at 27.5 °C.

Table 1 shows the quantitative results of the stereoselective crystallization of bevantolol hydrochloride in ethanol under the conditions described above; technical details of the process are given in the Section 4.

From Table 1 it is clear that the process of bevantolol hydrochloride separation is carried out with good enantiomeric purity of the crystalline precipitate (*ee* 92–96%) and high yields of pure enantiomers (23% in the first stage, then yield increases substantially). The degree of separation at the first step exceeds 50% (54.6% in fact), thereby creating a high enantiomeric enrichment of the mother liquor after the first crystallization cycle. At other stages, the degree of separation increases to 72–85% and the enantiomeric excess increases to ~32%.

In Figure 5, the bevantolol hydrochloride separation process (3 cycles, 6 runs), is illustrated by the values of optical rotation of the mother liquor. The red dots indicate the values of optical rotation at which the process was interrupted and the precipitate was filtered off. The missing amount of racemic **1** was then added to the mother liquor and the process was repeated (see Section 4).

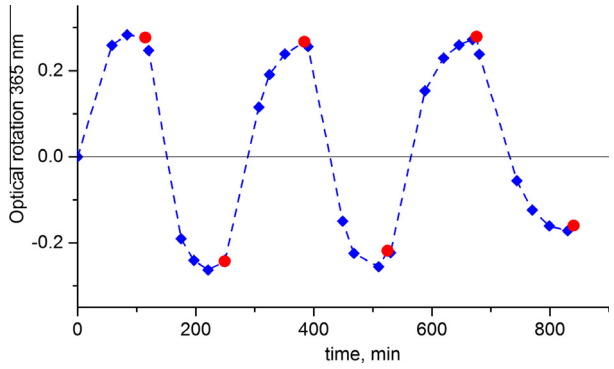

Figure 5. Mother liquor optical rotation vs time of preferential crystallization of bevantolol hydrochloride (3 cycles, 6 runs). Red dots—the value of optical rotation, on reaching which the process was interrupted; time spent on technical operations associated with the interruption and resumption of stereoselective crystallization process was not reflected in the chart.

In total, for three cycles (6 runs), from 11.20 g of *rac*-**1**, 2.763 g (24.7%) of (*S*)-**1** and 3.006 g (26.8%) of (*R*)-**1** were obtained. Figure 4c shows the possible trajectories of the resolution by entrainment process at the pseudo binary phase diagram of *rac*-**1** in water. Table 2 shows the quantitative results of this experiment. In total, 0.625 g (20.3%) of (*S*)-enantiomer and 0.599 g (19.4%) of (*R*)-enantiomer was obtained from 3.076 g from *rac*-**1** in three full cycles. It should be noted that although the yield of the pure enantiomers is somewhat higher in ethanol, in view of ecological requirements, the separation in water as a solvent is preferred.

3. Conclusions

In investigating the solubility of the active chiral pharmaceutical ingredient bevantolol hydrochloride **1** in various solvents, it can be seen that when *rac*-**1** is dissolved in ethanol or water, it meets the requirements of Meyerhoffer's rule. This property makes it possible to reduce the ternary phase diagram, which describes the solubility of chiral compound **1**, to pseudo binary phase diagram, which facilitates a qualitative and quantitative analysis of crystallization processes caused by temperature changes. The process of the resolution of *rac*-**1** is highly reproducible, does not require enantiomeric pre-enrichment of the racemate in the first cycle, and allows us to obtain crystalline precipitates with high enantiomeric purity in each run. Furthermore this method can be 'green' by using water as the solvent.

4. Experimental

4.1. General

The NMR spectra were recorded on a Bruker Avance-500 spectrometer (500.13 MHz for ^{1}H) in $CDCl_3$ with the signals of

Table 2
Resolution by entrainment of *rac*-bevantolol hydrochloride in water (50 ml, 10 mg of crystal seeds on every run, crystallization temperature 35.5 ± 0.5 °C)

Run	Added amount of *rac*-**1**, g	Operation amount of enantiomers, g		Resolution time, min	(*R*)-**1** and (*S*)-**1** obtained				
					Yield, g	*ee*[a], %	*YE*[b]		*DR*[c], %
		(*R*)-**1**	(*S*)-**1**				g	%	
1	2.300	1.150	1.150	60	(*R*) 0.232	93.6	0.207	18.0	69
2	0.222	1.048	1.252	80	(*S*) 0.252	90.1	0.217	17.3	72
3	0.242	1.155	1.145	90	(*R*) 0.276	92.6	0.246	21.3	82
4	0.266	1.033	1.267	80	(*S*) 0.255	91.4	0.223	17.6	74
5	0.245	1.143	1.157	90	(*R*) 0.279	89.7	0.241	21.1	80
6	0.269	1.023	1.267	80	(*S*) 0.417	70.4	0.284	22.4	95

[a] *ee*: enantiomeric excess (HPLC).
[b] *YE*: Yield enantiomer; *YE*(g) = [Yield(g) × *ee* (%)]/100 − 0.010; *YE*(%) = [*YE*(g) × 100]/Operation amount of (*R*)- or (*S*)-**1**(g).
[c] *DR*: degree of resolution; *DR* (%) = *YE*(g) · 100/[0.5 · (2.3–1.7)]; 1.7—solubility *rac*-**1** in 50 ml water at 35.5 °C.

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the solvent as the internal standard. 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. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter (concentration *c* is given as g/100 ml). The enantiomeric excess (*ee*) of the substances and intermediate samples used was checked by HPLC; HPLC analyses were performed on a Shimadzu LC-20AD system controller.

4.2. Compounds

Racemic epichlorohydrin *rac*-**3**, *meta*-cresol and 3,4-dimethoxyphenylethylamine were commercially available. Enantiopure epichlorohydrins (*R*)-**3** and (*S*)-**3** was prepared via the Jacobsen kinetic hydrolytic resolution of *rac*-**3**. (*R*)-**3**: bp 113–114 °C; $[\alpha]_D^{20} = -33.1$ (*c* 4, MeOH), 96% ee [chiral HPLC analysis; Chiralpack AD (0.46 × 25 cm) column; column temperature 20 °C; eluent: hexane/isopropanol = 9:1; flow rate: 1.0 ml/min; refractive index detector; $t_R = 7.5$ min]. (*S*)-**3**: $[\alpha]_D^{20} = +33.3$ (*c* 4, MeOH), 96% ee (chiral HPLC analysis; $t_R = 9.7$ min).

4.2.1. 1,2-Epoxy-3-(3-methylphenoxy)propane *rac*-2

To a solution of *rac*-**3** (51.36 g, 0.555 mol) and *m*-cresol (20.09 g, 0.185 mol), aqueous 2 M NaOH solution (130 ml) was added dropwise at 60 °C, after which the reaction mixture was stirred for 2 h at 60 °C. Then the reaction mixture was extracted with ether, and the combined organic portions were dried ($MgSO_4$) and concentrated. The residue was purified by distillation to yield *rac*-**2** (21.43 g, 71%) as a colorless oil, bp 100–105 °C at 0.1 mm Hg. ^{1}H NMR δ: 2.36 (s, 3H, CH_3), 2.78 (dd, J = 5.0, 2.7 Hz, 1H, CH_2), 2.92 (t, J = 4.5 Hz, 1H, CH_2), 3.36–3.38 (m, 1H, CH), 3.99 (dd, J = 11.0, 5.6 Hz, 1H, OCH_2), 4.22 (dd, J = 11.0, 3.3 Hz, 1H, OCH_2), 6.75–6.78 (m, 2H, $C^{2,4}{}_{Ar}H$), 6.82 (d, J = 7.5 Hz, 1H, $C^{6}{}_{Ar}H$), 7.25 (t, J = 7.8 Hz, 1H, $C^{5}{}_{Ar}H$).

4.2.1.1. (*S*)-1,2-Epoxy-3-(3-methylphenoxy)propane (*S*)-2. This compound was obtained from (*R*)-epichlorohydrin (*R*)-**3** (8.32 g, 0.09 mol) and *m*-cresol (3.89 g, 0.036 mol) as described for racemic compound. The configuration of the product is inverted as against the configuration of the starting epichlorohydrin; colorless oil (3.90 g, 66%), $[\alpha]_D^{20} = +13.1$ (*c* 1.7, MeOH). ^{1}H NMR δ: 2.36 (s, 3H, CH_3), 2.78 (dd, J = 4.9, 2.7 Hz, 1H, CH_2), 2.92 (dd, J = 4.9, 4.3 Hz, 1H, CH_2), 3.35–3.37 (m, 1H, CH), 3.99 (dd, J = 11.0, 5.5 Hz, 1H, OCH_2), 4.21 (dd, J = 11.0, 3.3 Hz, 1H, OCH_2), 6.74–6.78 (m, 2H, $C^{2,4}{}_{Ar}H$), 6.82 (dd, J = 7.4, 0.7 Hz, 1H, $C^{6}{}_{Ar}H$), 7.14 (t, J = 7.8 Hz, 1H, $C^{5}{}_{Ar}H$).

4.2.1.2. (*R*)-1,2-Epoxy-3-(2-methylyphenoxy)propane (*R*)-2. This compound was synthesized analogously from (*S*)-**3**; colorless oil; $[\alpha]_D^{20} = -12.9$ (*c* 1.0, MeOH).

4.2.2. *rac*-1-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-3-(3-methylphenoxy)-2-propanol hydrochloride, *rac*-Bevantolol hydrochloride, *rac*-1

This compound was prepared by analogy with a previously described procedure.[38,30] *rac*-1,2-Epoxy-3-(3-methylphenoxy)-propane *rac*-**2** (21.0 g, 0.128 mol) and 23.2 g (0.128 mol) of 3,4-dimethoxyphenethylamine in 50 ml of ethanol were stirred at 25–30 °C for 24 h. The reaction was monitored by TLC. After the 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 37.5 g (75%) of crude *rac*-**1**·HCl. After recrystallization from CH_3CN/EtOH (9:1) was obtained 26.4 g (54%) of *rac*-**1**·HCl: white solid, mp 140–141 °C. ^{1}H NMR δ: 2.29 (s, 3H, CH_3), 3.21–3.37 (m, 6H, $CH_2N^+CH_2CH_2$), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.97 (dd, J = 9.7, 5.9 Hz; 1H, $1OCH_2$), 4.06 (dd, J = 9.7, 4.3 Hz; 1H, $1OCH_2$), 4.69 (m, 1H, OCH), 5.26 (broad s, OH), 6.63–6.67 (m, 2H, Ar), 6.76–6.81 (m, 4H, Ar), 7.12 (t, J = 7.8 Hz, 1H, Ar), 8.90 (broad s, N^+H), 9.80 (broad s, 1H, N^+H).

The samples of enantiopure bevantolol hydrochloride, which were used as seeds, were obtained according to the literature:[30] (*R*)-**1**: mp 157–158 °C; $[\alpha]_D^{20} = +19.3$ (*c* 1.1, EtOH); 99.8% *ee* [chiral HPLC analysis; Daicel Chiralcel OD-RH (0.46 × 25 cm) column; column temperature 24 °C; eluent KPF_6 aq (0.05 M pH 2.1): CH_3CN = 60:40 v/v; flow rate: 0.7 ml min^{-1}; UV detector 254 nm; $t_R = 8.8$ min]. (*S*)-**1**: mp 157–158 °C; $[\alpha]_D^{20} = -19.2$ (*c* 1.1, EtOH); 99.9% *ee* (chiral HPLC analysis; $t_R = 13.3$ min). NMR spectra were identical with those published earlier.[30]

4.3. Solubility measurement

In order to determine the solubility, the polythermal laser monitoring last crystal disappearance method was used. Precisely controlled samples [Shimadzu AUW 120D analytic balance (accuracy ± 0.01 mg)] of *rac*-**1** and (*S*)-**1** in 1 ml of solvent were placed in sealed glass vessels, equipped with magnetic stir bar. For more precise temperature control in the vicinity of the test samples a vessel equipped with a controlling thermometer, a stir bar and a solvent were placed. All the vessels were placed in a thermostatic container. The suspension of the samples was agitated at about 400 rpm, increasing the temperature gradually (0.5 °C/min). The turbidity degree was registered for each individual reactor to detect the so-called 'clear point'. The temperature where the last crystals disappeared was taken as saturation temperature. After complete dissolution of the crystals in all the studied reactors the coolant was slowly cooled down (~0.3 °C/min), detecting the so-called 'cloud points' (the temperature where the first crystals were reliably detected) in cooling cycles.

4.4. Preferential crystallization

Experiments on the stereoselective crystallization of *rac*-**1** were performed in a three-necked flask equipped with a magnetic stirrer, water condenser and thermometer placed in a water bath at a controlled temperature. During the resolution small portions of the mother liquor were taken through a syringe equipped with Teflon filter and were analyzed either by polarimetry (the case of EtOH as resolution solvent; cell path length 100 mm; wavelength 365 nm; 20 °C), or by HPLC (the case of water).

Example of the resolution by entrainment of racemic bevantolol hydrochloride in ethanol without the initial enantiomeric enrichment of a starting mixture: 6.07 g of (*RS*)-**1** was dissolved in 100 ml of EtOH (96%) at 38–40 °C and was cooled with stirring to 28 °C. Then a portion of finely ground crystalline seeds of (*S*)-bevantolol hydrochloride (10 mg, 0.17% by weight) was added. The solution was stirred and incubated at a temperature of 27.5 ± 0.5 °C for 120 min. The precipitate was filtered, collected and dried to obtain 750 mg of (*S*)-bevantolol (*ee* 94.9%). To the filtrate, which remained after separation of the precipitate, 740 mg of (*RS*)-bevantolol were added, and the system was heated to 38–40 °C until full homogenization after which it was cooled to 28 °C, and seeded with finely ground crystals of (*R*)-bevantolol hydrochloride (10 mg). The solution was stirred at a temperature of 27.5 ± 0.5 °C, and filtered after 130 min; 1170 mg of (*R*)-bevantolol, *ee* 94.7%, were obtained. Likewise, the cycle was repeated several times, each time adding the lacking amount of racemic bevantolol hydrochloride. Details of subsequent runs No. 3–6 are shown in Table 1. A single recrystallization of the combined crystal crop of each of the enantiomers from acetonitrile enhances the enantiomeric excess to 99%.

Experiment on *rac*-**1** separation in water was performed similarly without enantiomeric enrichment. Experimental details are given in Table 2.

Acknowledgments

The authors thank the Russian Fund of Basic Research and the Government of the Republic of Tatarstan for financial support (Grant No. 15-43-02238). We also wish to thank Dr. A.V. Pashagin for valuable assistance with chiral HPLC analysis.

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