Convenient Preparation of Enantiopure Atenolol by Means of Preferential Crystallization

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Received September 2, 1997; accepted November 10, 1997

(*R*)- or (*S*)-Atenolol (1) in enantiopure form was prepared in an extremely simple way. Atenolol of *ca.* 95% ee was prepared in one-pot from *p*-hydroxyphenylacetamide (2) and (*R*)- or (*S*)-epichlorohydrin (3). Then, preferential crystallization of the Brønsted's acid salts of the resulting atenolol improved the enantiomeric purity up to 99.8% ee.

Key words optically active atenolol; optically active epichlorohydrin; preferential crystallization; β-adrenergic blocking agent

Atenolol is widely used for the treatment of hypertension and angina, and may be applicable for the treatment of post myocardial infarction.[1] Only the racemate has been commercially available so far, although a lowered heart rate is sometimes encountered after administration of the racemate. Use of the (*S*)-enantiomer avoids this side effect.[2] Thus, preparation of atenolol in enantiopure form is of great significance, yet only a few reports have appeared on this subject.[3,4]

Both (*R*)- and (*S*)-3-tosyloxy-1,2-propanediol acetonides, which were prepared from D-mannitol, were employed in the synthesis of atenolol of 79% ee. Later, enzymatic kinetic resolution was invoked to obtain a key intermediate, 1-[*p*-[(butoxycarbonyl)methyl]phenoxy]-3-chloropropan-2-ol, which finally gave atenolol in 95% ee. Racemic atenolol and its analogs were prepared by the reaction of *p*-hydroxyphenylacetamide with an excess of racemic epichlorohydrin followed by treatment of the resulting glycidyl ether with isopropyl amine.[5] Nevertheless, use of enantiopure epichlorohydrin failed to afford the glycidyl ether with satisfactory enantiomeric purity (<70% ee). Moreover, another disadvantage is that the recovered epichlorohydrin cannot be re-used because of its decreased enantiomeric purity.

Previously, we disclosed a new method to obtain enantiopure atenolol (**1**) starting from (*R*)- and (*S*)-epichlorohydrins (**3**),[6] which have recently become commercially available. *p*-Hydroxyphenylacetamide (**2**) was allowed to react with **3** and the resulting 4-(carbamoylmethyl)phenyl glycidyl ether (**4**) was treated with isopropylamine. In this process, repeated recrystallization of **4** is crucial to attain **1** of high enantiomeric purity.[7] When **4** with a lower level of enantiomeric purity was subjected to the reaction with isopropylamine, it was difficult to improve the enantiomeric purity of the resulting atenolol by simple recrystallization. Consequently, the one-pot synthesis of **1** from **2** and **3** was not practical. The present study stemmed from our expectation that development of new technology to increase the enantiomeric purity of atenolol would allow direct access to enantiorich **1**.

As shown in Chart 1, **2** was treated with 1.1 molar eq of (*R*)- or (*S*)-**3** in the presence of sodium hydroxide (1.0 eq) and a catalytic amount of benzyltrimethylammonium chloride (BTA) to afford a mixture of **4** and **5**. The mixture, without isolation, was exposed to a large excess of isopropylamine to give atenolol in 90% yield with 95% ee. Attempts to further improve the % ee by recrystallization failed, because the difference in solubility between the racemic and enantiopure forms of atenolol was too small.

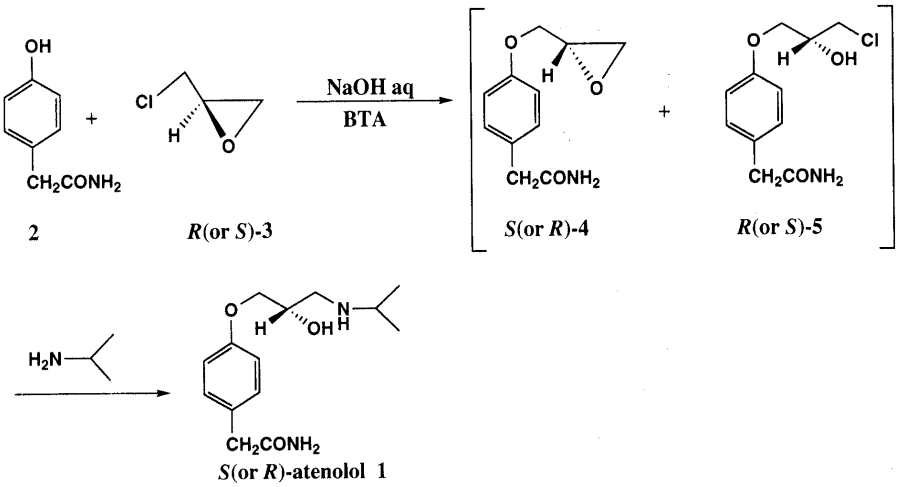

Chart 1

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We then turned our attention to preferential crystallization.[8] It seemed to us that conversion of atenolol to salts with acids would increase the difference of solubility between the racemic and enantiopure forms. As we expected, the salts with Brønsted's acids exhibited a much greater difference in solubility. The solubility data for the enantiopure and racemic salts are summarized in Table 1.

With these data in hand, the preferential crystallization was addressed. A solution of atenolol and an acid in a suitable solvent was stirred at room temperature for a suitable period. The precipitates formed were filtered off and the filtrate was concentrated to give atenolol salts of high enantiomeric purity. The employment of benzoic acid in chloroform and *p-tert*-butylbenzoic acid in chloroform resulted in the formation of virtually enantiopure atenolol salts (99.3—99.4% ee). The highest level of enantiopurity (99.8% ee) was attained by the use of *p*-toluic acid in acetone.

Unsatisfactory ee's were obtained with HCl in iso-PrOH, *p*-toluic acid in EtOH or $CHCl_3$, and *p*-toluenesulfonic acid in EtOH (Table 2). These results can be well correlated with the solubilities, as given in Table 1. The systems with a solubility ratio larger than 100 allow satisfactory preferential crystallization, while poorer enantiomeric purities were attained in the systems with a solubility ratio smaller than 50. It is noteworthy that pure atenolol was readily recovered from the salts by exposure to ion exchange resin (Amberlyst 15H).

Table 1. The Solubility of Optically Active Atenolol and Racemic Salt

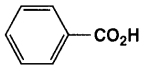
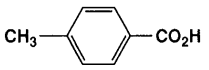
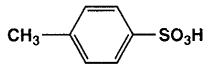
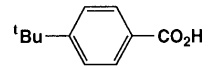
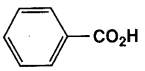
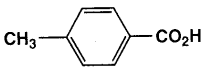
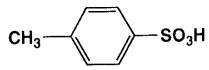
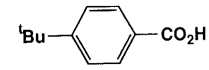
Acid	Solvent	Solubility (g/ml at 25 °C)	
		Optical active salt (*R*/*S*)	Racemic salt
HCl	iso-PrOH	1.16 (*R*)	0.09
	$CHCl_3$	3.43 (*S*)	0.02
	EtOH	2.28 (*S*)	0.67
	Acetone	1.58 (*R*)	0.01
	Acetone	1.64 (*S*)	0.01
	$CHCl_3$	3.50 (*S*)	0.07
	EtOH	0.63 (*R*)	0.03
	$CHCl_3$	2.75 (*R*)	0.02

Table 2. Preferential Crystallization with Various Acids

Acid	Solvent	Atenolol		Atenolol salt	
		R/*S*	% ee[a]	Filtrate (% ee)[a]	Precipitate (% ee)[a]
HCl	iso-PrOH	*R*	90.3	92.5	87.5
	$CHCl_3$	*S*	94.4	99.4	76.7
	EtOH	*S*	71.1	80.2	59.7
	Acetone	*R*	79.2	99.4	71.1
	Acetone	*S*	94.8	99.8	81.8
	$CHCl_3$	*S*	98.1	99.0	56.5
	EtOH	*R*	92.4	94.1	86.6
	$CHCl_3$	*R*	96.0	99.3	78.9

a) As atenolol based on HPLC on a Daicel Chiralcel OD column with hexane–EtOH–Et_2NH (90 : 10 : 0.1), 1.0 ml/min; retention times, 14.0, 17.9 min.

Table 3. Physical Properties of Optically Active Atenolol Salts

R/*S*	Atenolol salt	Yield (%)	mp (°C)	% ee[a]	$[\alpha]_D^{21}$ (*c* = 1.0, MeOH)	Formula	Elemental analysis (%) Calcd (Found)		
							C	H	N
S	*p*-Toluate	86.4	116.4—120.7	99.8	−14.8°	$C_{22}H_{30}N_2O_5$	65.65	7.52	6.96
							(65.77	7.53	6.97)
R	*p*-Toluate	70.3	119.5—124.3	99.4	+14.6°	$C_{22}H_{30}N_2O_5$	65.65	7.52	6.96
							(65.80	7.54	6.97)
S	Hydrochloride	46.7	149.4—152.5	93.5	−23.0°	$C_{14}H_{23}ClN_2O_3$	55.53	7.66	9.25
							(55.70	7.68	9.24)
R	Hydrochloride	43.4	149.6—151.6	92.5	+22.6°	$C_{14}H_{23}ClN_2O_3$	55.53	7.66	9.25
							(55.55	7.68	9.24)
S	Benzoate	80.0	119.0—121.8	99.4	−15.6°	$C_{21}H_{28}N_2O_5$	64.93	7.26	7.21
							(65.08	7.27	7.23)
R	Benzoate	81.5	116.8—120.2	99.2	+15.4°	$C_{21}H_{28}N_2O_5$	64.93	7.26	7.21
							(65.01	7.26	7.23)
S	*p*-Toluenesulfonate	54.4	117.6—123.0	96.0	−14.7°	$C_{21}H_{30}N_2O_6S$	57.52	6.89	6.39
							(57.38	6.80	6.40)
R	*p*-Toluenesulfonate	48.5	113.1—122.8	94.1	+14.2°	$C_{21}H_{30}N_2O_6S$	57.52	6.89	6.39
							(57.60	6.91	6.36)
S	*p-tert*-Butylbenzoate	72.8	162.9—165.1	98.9	−14.1°	$C_{25}H_{36}N_2O_5$	67.54	8.16	6.30
							(67.70	8.18	6.28)
R	*p-tert*-Butylbenzoate	80.6	163.1—166.6	99.3	+14.5°	$C_{25}H_{36}N_2O_5$	67.54	8.16	6.30
							(67.72	8.18	6.33)

a) As atenolol based on HPLC on a Daicel Chiralcel OD column with hexane–EtOH–Et_2NH (90 : 10 : 0.1), 1.0 ml/min; retention times, 14.0, 17.9 min.

In conclusion, a short process for obtaining higly enantiopure atenolol of 99.3—99.8% ee has been established. It is of great significance that atenolol can be prepared in one-pot from commercially available starting materials. Moreover, preferential crystallization is highly advantageous compared with optical resolution, another possible technology to increase the enantiomeric purity, because the latter method requires chiral auxiliaries to form diastereomers. In these respects, the present process is highly favorable for producing enantiopure atenolol.

Experimental

Melting points were determined with a Mettler FP-61 melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM-GSX-270 NMR spectrometer with tetramethylsilane as an internal standard. HR-MS were recorded on a JEOL JMS-AX505W. Optical rotations were measured on a JASCO DIP-370 at 21 °C. All reactions were monitored by HPLC. Elemental analyses were done using a Yanaco CHN-MT-3 apparatus. HPLC analyses were performed on a DAISO PACK SP-120-5-ODS-AP column (4.6 mm i.d. × 150 mm) using a Shimadzu LC-5A system equipped with an SPD-6A UV detector (eluent, MeOH–H_2O containing 2 mM 1-octanesulfonic acid sodium salt, 7 : 3, v/v; flow rate, 1.0 ml/min; detection, UV at 228 nm; temperature, 40 °C). Enantiomeric excesses were determined by HPLC on a Chiralcel OD column (4.6 mm i.d. × 250 mm, eluent, hexane–EtOH–Et_2NH, 90 : 10 : 0.1 v/v; flow rate, 1.0 ml/min; UV at 228 nm; temperature, 30 °C).

Preparation of (*S*)-Atenolol (1) A mixture of (*R*)-epichlorohydrin (**3**) (24.4 g, 0.26 mol, 98.9% ee) and H_2O (21 ml) was stirred under cooling at 5 °C. To it was added dropwise a solution of **2** (35.7 g, 0.24 mol), benzyltrimethylammonium chloride (0.18 g) and NaOH (9.6 g, 0.24 mol) in H_2O (158 ml) over a period of 1 h. The mixture was stirred at 5 °C for 20 h and then neutralized with 3.5% HCl. The reaction mixture was added to isopropylamine (334 g, 5.76 mol) at 10 °C with stirring over a period of 1 h, and the solution was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure. The precipitates were dissolved in AcOEt, washed with H_2O and evaporated to give crude (*S*)-**1** (57.5 g). Recrystallization from AcOEt to give (*S*)-**1** (53.9 g, 90%, 94.8% ee).

Preparation of (*R*)-Atenolol (1) (*R*)-Atenolol was synthesized from (*S*)-epichlorohydrin (**3**) (99.0% ee) in 89% yield by the same procedure as that used for (*S*)-**1** (94.3% ee).

Preferential Crystallization Procedure, Preparation of (*S*)-Atenolol *p*-Toluate Crude (*S*)-atenolol (4.43 g, 16.65 mmol, 94.8% ee) and *p*-toluic acid (2.28 g, 16.76 mmol) were dissolved in acetone (300 ml), and the solution was stirred at room temperature for 12 h. The precipitated crystals were collected by filtration, and the filtrate was concentrated under reduced pressure to give (*S*)-atenolol *p*-toluate (5.62 g, 86.4%, 99.8% ee) as colorless prisms. mp 116.4—120.7 °C, $[\alpha]_D^{21} = -14.8°$ ($c = 1.0$, MeOH). *Anal.* Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.52; N, 6.96. Found: C, 65.77; H, 7.53; N, 6.97.

Preparation of (*R*)-Atenolol *p*-Toluate (*R*)-atenolol *p*-toluate, colorless prisms, was synthesized from (*R*)-**1** (79.2% ee) in 70.3% yield by the same procedure as that used for (*S*)-atenolol *p*-toluate. 99.4% ee, mp 119.5—124.3 °C, $[\alpha]_D^{21} = +14.6°$ ($c = 1.0$, MeOH). *Anal.* Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.52; N, 6.96. Found: C, 65.80; H, 7.54; N, 6.97.

General Procedure for Recovery of Atenolol from the Salts (*S*)-Atenolol (1) (*S*)-Atenolol *p*-toluate (5.62 g, 14.0 mmol, 99.6% ee) was treated with ion exchange resin (Amberlyst 15H) to give enantiomerically pure (*S*)-**1** (3.48 g, 93.5%, 99.8% ee) as colorless prisms. mp 153.7—154.4 °C, $[\alpha]_D^{21} = -17.5°$ ($c = 1.0$, 1 N HCl). HR-MS *m/z*: 266.1630 (Calcd for $C_{14}H_{22}N_2O_3$: 266.1629).

(*R*)-Atenolol (1) (*R*)-Atenolol **1**, colorless prism, was recovered from (*R*)-atenolol *p*-toluate (99.4% ee) in 90% yield by the same procedure as that used for (*S*)-**1**. 99.6% ee, mp 153.5—154.4 °C, $[\alpha]_D^{21} = +17.4°$ ($c = 1.0$, 1 N HCl). HR-MS *m/z*: 266.1630 (Calcd for $C_{14}H_{22}N_2O_3$: 266.1629).

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