An Improved Process of Separation of *R*- and *S*-Timolol

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Diastereomeric timolol tartrates **4** are obtained in a one-pot synthesis from the racemic base **2** and optically active *O,O*-diacetyl- or *O,O*-dibenzoyltartaric anhydrides **3**, as only one of the diastereomers precipitates from acetone solution. Acidic hydrolysis as the corresponding **4** leads to timolol in high yield and optical purity.

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(*S*)-3-Morpholino-4-(3-*tert*-butylamino-2-hydroxypropyl)oxy-1,2,5-thiadiazole maleate **1** (timolol maleate) was developed as a β-adrenergic blocking agent, and was introduced into human therapy for the treatment of mild to moderate essential hypertension and angina pectoris [1]. Later, in the form of eye drops, timolol proved very effective in the medication of glaucoma, and it became a first-line drug in this field [2,3].

As the biological activity of β-adrenergic blocking agents resides mainly in one of the enantiomers, intense research was performed to prepare optically pure (*S*)-timolol **1** by asymmetric synthesis [4-6], chiral separation of racemic timolol into its enantiomers by means of chromatography [7-10], diastereomeric salt formation and fractional crystallization [11,12], or separation of diastereomeric covalent derivatives of timolol by either chromatography [13-15] or crystallization [16,17].

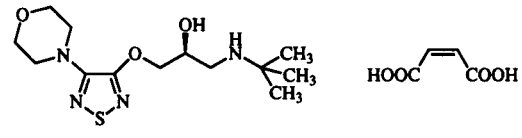
Although different asymmetric syntheses [4-6] have been elaborated for the preparation of (*S*)-timolol **1**, the resolution of racemic timolol **2** remains an economically alternative route, because of the low availability of **2**, and the high cost and in some cases the instability of the intermediates used in its asymmetric syntheses. Effective methods have also been developed for the racemization of (*R*)-timolol [18,19].

An attractive method for the separation of **2** is esterification with *O,O*-dialkanoyl- or *O,O*-diaroyl-(*R,R*)-tartaric acid anhydride **3**, and fractional crystallization of the diastereomeric mixture of *O*-monoesters, followed by acidic or basic hydrolysis of the isolated **4** [16]. Accordingly, **2** was reacted with either *O,O*-diacetyl- or *O,O*-dibenzoyl-(*R,R*)-tartaric acid anhydride **3** in methylene dichloride at ambient temperature for 15 minutes. After evaporation of the organic solvent, the residue was crystallized from acidified aqueous methanol for 20 hours. Repeated crystallization gave *ca* 70% of (*S*)-timolol *O*-monoesters **4** in 97% optical purity. Finally, the desired enantiomer **1** was liberated in quantitative yield from **4** (R = Me or Ph) by acidic or basic hydrolysis.

This derivatization method was simplified by combining the esterification and resolution steps by using acetone instead of methylene dichloride. When **2** was reacted with **3** (R = Me or Ph), in acetone at room temperature for 2-20 hours, the pure *O*-monoester **4**, (R = Me or Ph) precipitated from the reaction mixture, while the other diastereomer remained in the solvent. After filtration, the *O*-monoester **4** (R = Me or Ph) was obtained in high optical purity (≥98%) in 73-80% yield.

The other diastereomer can be obtained from the filtrate after evaporation, with lower optical purity, or by using the enantiomer of **4a** (R = Ph) prepared from *O,O*-dibenzoyl-(*S,S*)-tartaric acid [20]. From the antipodes of the *O*-monoesters, the optically active timolol enantiomers are readily recovered by hydrolysis.

The products gave satisfactory combustion analyses and were characterized by mp, ^{1}H-nmr spectroscopy, optical purity examination and optical rotation data.



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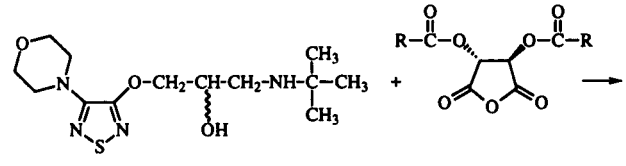
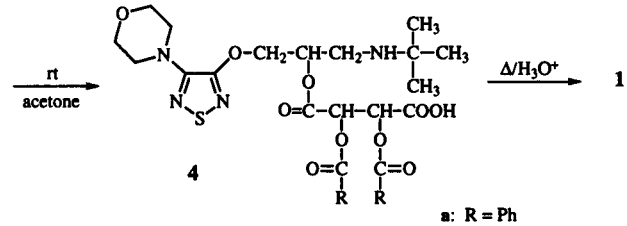


2 **3**



4

EXPERIMENTAL

The ^{1}H-nmr spectra were measured in deuteriochloroform on a Bruker DRX-400 spectrometer at 400.13 MHz. Chemical shifts are given on the δ scale, and TMS was used as internal standard. The diastereomeric purity of *O*-monoesters was determined by hplc on a Hypersil BDS 3 C8 column; eluent: 17:83 = acetonitrile:50 m*M* ammonium dihydrogen orthophosphate buffer (pH 3), k' = 4.3 and 9.1 for the (*S*)-(*R,R*) and (*R*)-(*R,R*) diastereomers, respectively, of **4a**; 32:68 = acetonitrile:50 m*M* ammonium dihydrogen orthophosphate buffer (*p*H 3), k' = 4.7 and 6.8 for the (*S*)-(*R,R*) and (*R*)-(*R,R*) diastereomers, respectively, of **4b**.

(*S*)-1-*tert*-Butylamino-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propyl 2,3-(*O,O*-Dibenzoyl)-(*R,R*)-monotartrate (**4a**, R = Ph).

To a stirred solution of 3.16 g (10 mmoles) of **2** in 316 ml of acetone was added 4.1 g (12 mmoles) of *O,O*-dibenzoyl-*R,R*-tartaric acid anhydride **3** (R = Ph). The reaction mixture was stirred at room temperature for 2 hours. The crystals which precipitated were filtered, washed once with ice-cold acetone and dried, provided 2.72 g (84%) of **4** (R = Ph), mp 217-219°; ^{1}H-nmr (deuteriochloroform + DMSO-d_6): 1.46 s (9H, 3 x CH_3), 3.18 dd (1H, NCH_a, $^2J_{Ha,Hb}$ 13.5, and $^3J_{Ha,CH}$ 2.5 Hz), 3.23 dd (1H, NCH_b, $^3J_{Hb,CH}$ 9.3 Hz), 3.46 (4H, CH_2NCH_2), 3.73 (4H, CH_2OCH_2), 4.68 d (2H, OCH_2, $^3J_{CH2,CH}$ 4.7 Hz), 5.51 d and 5.58 d (1H + 1H, OCCHCHCO, $^3J_{CH,CH}$ 8.1 Hz), 5.57 m (1H, CH_2CHCH_2), 7.42, 7.57, and 8.09 (4H + 2H + 4H, 2 x Ph), and 9.7 ppm (2H, NH_2^+); $[\alpha]_D$ = +8.2° (c = 6, acetic acid); optical purity: 98.4%.

(*R*)-1-*tert*-Butylamino-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propyl 2,3-(*O,O*-Dibenzoyl)-(*S,S*)-monotartrate.

To a stirred solution of 3.16 g (10 mmoles) of **2** in 316 ml of acetone 4.1 g (12 mmoles) of *O,O*-dibenzoyl-*S,S*-tartaric acid anhydride was added. The reaction mixture was stirred at room temperature for 2 hours. The crystals which precipitated were filtered, washed once with ice-cold acetone and dried, provided 2.4 g (74%) of (*R*)-1-*tert*-butylamino-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propyl 2,3-(*O,O*-dibenzoyl)-(*S,S*)-monotartrate, mp 221-222°; $[\alpha]_D$ = -8.3° (c = 6, acetic acid); optical purity (hplc): 98.4%.

(*S*)-1-*tert*-Butylamino-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propyl 2,3-(*O,O*-Diacetyl)-(*R,R*)-monotartrate (**4b**, R = Me).

To a stirred solution of 3.16 g (10 mmoles) of **2** in 79 ml of acetone 2.6 g (12 mmoles) of *O,O*-diacetyl-*R,R*-tartaric acid anhydride **3** (R = Me) was added. The reaction mixture was stirred at room temperature for 20 hours. The crystals which precipitated were filtered, washed with ice-cold acetone and dried, provided 1.93 g (73%) of (+)-**4** (R = Me), mp 214-215°; ^{1}H-nmr (deuteriochloroform): 1.46 s (9H, 3 x CH_3), 2.05 s and 2.16 s (3H + 3H, 2 x $COCH_3$), 3.16 dd (1H, NCH_a, $^2J_{Ha,Hb}$ 13.1, and $^3J_{Ha,CH}$ 1.7 Hz), 3.22 dd (1H, NCH_b, $^3J_{Hb,CH}$ 9.9 Hz), 3.5 (4H, CH_2NCH_2), 3.8 (4H, CH_2OCH_2), 4.57 dd (1H, OCH_a, $^2J_{Ha,Hb}$ 12.3, and $^3J_{CH2,CH}$ 4 Hz), 4.61 dd (1H, OCH_b, $^3J_{CH2CH}$ 5 Hz), 5.06 d and 5.10 d (1H + 1H, OCCHCHCO, $^3J_{CHCH}$ 8.2 Hz), 5.31 m (1H, CH_2CHCH_2), 9.7 (1H, NH) and 11.1 ppm (1H, OH); $[\alpha]_D$ = +21° (c = 6, acetic acid); optical purity (hplc): 98.3%.

(*S*)-3-Morpholino-4-(3-*tert*-butylamino-2-hydroxypropyl)oxy-1,2,5-thiadiazole (*S*-Timolol).

Compound (+)-**4** (R = Ph) (6.57 g, 10 mmoles) was refluxed in 220 ml of 10% sulfuric acid solution for 10 hours. After the hydrolysis was completed, the *p*H of the solution was slowly adjusted to 10-11 with 10 *N* sodium hydroxide solution, the temperature being kept below 20°. The reaction mixture was extracted with diethyl ether. The organic phase was washed with water, and dried over anhydrous sodium sulfate. After evaporation of the solvent in vacuum, 3.14 g (*ca* 100%) of *S*-timolol was obtained as a colorless oil, mp (maleate) 201-204°; lit [3] mp 199-201°; $[\alpha]_{405}$ (maleate) = -12.3° (c = 3, 1 *N* hydrochloric acid); lit [21] $[a]_{405}$ = -11.7-12.5° (c = 5, 1 *N* hydrochloric acid).

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