Synthesis and Biological Activities of Optically Active 6-[3-(3,4-Dimethoxybenzylamino)-2-hydroxypropoxy]-2(1*H*)-quinolinone (OPC-18790)

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The enantiomers of 6-[3-(3,4-dimethoxybenzylamino)-2-hydroxypropoxy]-2(1*H*)-quinolinone (OPC-18790), a novel cardiotonic agent, were synthesized and evaluated for positive inotropic activity. The key intermediates, 2,3-epoxypropoxy derivatives, were obtained by the alkylation of 6-hydroxy-2(1*H*)-quinolinone with optically active epichlorohydrin and subsequent ring closure.

In an *in vitro* study, the (*R*)-(+)-isomer was about 10-fold more potent than the (*S*)-(−)-isomer.

Key words OPC-18790; optically active epichlorohydrin; cardiotonic agent; 2(1*H*)-quinolinone; positive inotropic activity

In a previous paper,[2)] we reported the synthesis and biological activities of 6-(3-amino-2-hydroxypropoxy)-2(1*H*)-quinolinone derivatives and related compounds. Among them, (±)-6-[3-(3,4-dimethoxybenzylamino)-2-hydroxypropoxy]-2(1*H*)-quinolinone (**1**, OPC-18790) (Fig. 1) was selected as a promising candidate for the treatment of congestive heart failure (CHF). This compound has an asymmetric center at the 2-position of the side chain and therefore has two enantiomers.

Among other positive inotropic agents for the treatment of CHF, denopamine[3)] acts through β-adrenoreceptors and SK&F 95654[4)] acts by inhibition of cardiac cyclic guanosine monophosphate (GMP)-inhibited phosphodiesterase. There is more than 100-hold difference in activity between the enantiomers of the former compound, and 80—100-fold difference in the case of the latters. Since **1** has no β-agonistic action and may act by prolonging the action potential duration and inhibiting cardiac cyclic GMP-inhibited phosphodiesterase,[5)] the possible differences in biological activity between the enantiomers is of interest. We describe here the synthesis and positive inotropic activity of the optical isomers of OPC-18790.

Synthesis Optically active β-amino alcohols of this type are usually prepared by the optical resolution of racemic compounds or by using chiral building blocks, for example, glycidyl tosylate, epichlorohydrin or 3-tosyloxy-1,2-propandiol acetonide and so on. In general, the former method is tedious, and the latter requires selective alkylation at the 6-position of 6-hydroxy-2(1*H*)-quinolinone (**2**). After some investigation of selective alkylation using chiral building blocks, we selected the method using optically active epichlorohydrin,[6)] as shown in Chart 1. Since epichlorohydrin offers two potential sites of electrophilic reactivity in this reaction, the intermediate 2-chloro-3-propoxy derivatives **3** must be isolated to avoid racemization.

Thus, alkylation of **2** with (*S*)-(+)-epichlorohydrin in the presence of triethylamine gave (*S*)-6-(3-chloro-2-hydroxypropoxy)-2(1*H*)-quinolinone (**3a**) in 71.5% yield. Compound **3a** was treated with KOH to give (*R*)-6-(2,3-epoxypropoxy)-2(1*H*)-quinolinone (**4a**) in 67.0% yield.

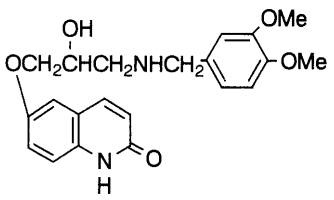
Finally, pure (*R*)-(+)-**1** was obtained in 72.5% yield by ring-opening reaction of **4a** with 3,4-dimethoxybenzylamine followed by a single recrystallization. The other isomer, (*S*)-(−)-**1**, was obtained similarly from **2** with (*R*)-(−)-epichlorohydrin *via* **3b** and **4b**. The optical purity of each enantiomer appeared to be almost 100% ee, as determined by the method of Sedman and Gal.[7,8)]

Pharmacology Both enantiomers were evaluated for positive inotropic activity in canine isolated blood-perfused heart preparations by the method reported previously.[2,5)] The results are shown in Fig. 2 together with comparative data for the racemate. From the ED_{25} values, the (*R*)-(+)-isomer appeared to be approximately 1.3 fold more potent than (±)-**1** and the (*S*)-(−)-isomer, approximately 7.9 fold less potent than (±)-**1**. The enantiomers showed about 10-fold difference in activity.

A more detailed study of the cardiovascular effects of these compounds will be reported elsewhere.

Conclusion We synthesized both enantiomers OPC-18790 [(*R*)-(+)-**1** and (*S*)-(−)-**1**] with high optical purity from **4a** and **4b**, respectively, which were obtained by the alkylation of **2** with optically active epichlorohydrin and subsequent ring closure reaction. Compared with denopamine (β-agonist) or SK&F 95654 (PDE inhibitor), these enantiomers showed a small difference in activity. OPC-18790 is currently undergoing clinical trial as a racemic mixture.

A high-performance liquid chromatographic (HPLC) assay method for the quantification of these compounds has already been reported by our colleagues.[9)]



1 (OPC-18790)

Fig. 1. Structure of OPC-18790

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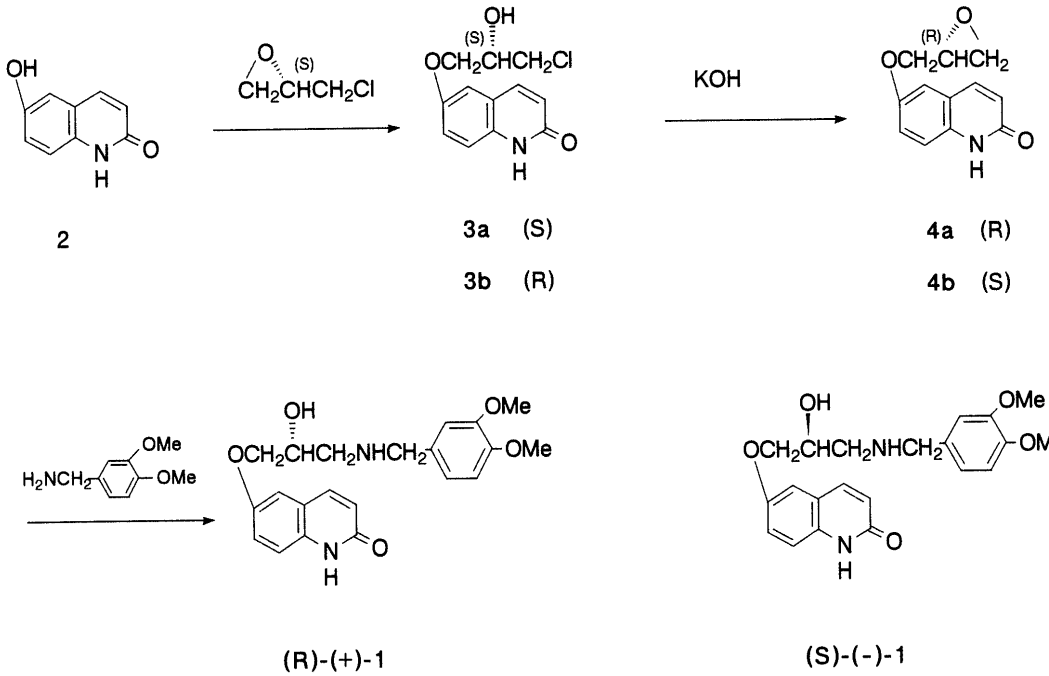

Chart 1

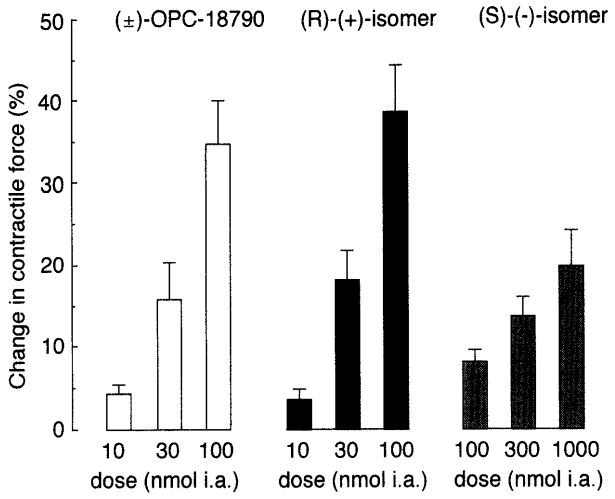

Fig. 2. Inotropic Effect of (±)-OPC-18790, (*R*)-(+)-OPC-18790 and (*S*)-(−)-OPC-18790 in Isolated Blood-Perfused Right Ventricular Papillary Muscle Preparation of Dog

Experimental

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer and Perkin Elmer 1600. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-200 or AC-250 or Varian XL-200 spectrometer operating at 200 or 250 MHz, respectively. Chemical shifts are reported in ppm, referenced to tetramethylsilane or DMSO-d_6 (0.00 and 2.50, respectively).

(*S*)-(+)-6-(3-Chloro-2-hydroxypropoxy)-2(1*H*)-quinolinone (3a) A mixture of 6-hydroxy-2(1*H*)-quinolinone (1.6 g, 9.9 mmol), (*S*)-(+)-epichlorohydrin (8 ml, 102.3 mmol) and Et_3N (0.71 ml, 5.1 ml) in MeOH (10 ml) and H_2O (10 ml) was stirred at room temperature overnight. After removal of (*S*)-(+)-epichlorohydrin, MeOH and H_2O by evaporation, the residue was triturated with H_2O and Et_2O. The resulting precipitates were collected by suction and purified by column chromatography (silica gel; CH_2Cl_2 : MeOH = 20 : 1—12 : 1) to afford **3a** (1.8 g, 71.5%), mp 198—200 °C. $[\alpha]_D^{20}$ +1.4° (*c* = 0.68, MeOH). NMR (DMSO-d_6) δ: 3.60—3.81 (2 H, m), 3.90—4.15 (3H, m), 5.58 (1H, d, *J* = 4.8 Hz,), 6.49 (1H, d, *J* = 9.6 Hz), 7.14—7.27 (3H, m), 7.84 (1H, d, *J* = 9.6 Hz), 11.6 (1H, br s). IR (KBr): 1663, 1622, 1429, 1243, 622 cm^{-1}. *Anal.* Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.92; H, 4.74; N, 5.36.

(*R*)-(−)-6-(3-Chloro-2-hydroxypropoxy)-2(1*H*)-quinolinone (3b) Compound **3b** (68.7%) was prepared by a procedure similar to that used for **3a**, mp 198—200 °C, $[\alpha]_D^{20}$ −1.5° (*c* = 0.68, MeOH). *Anal.* Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.83; H, 4.74; N, 5.40. The IR and NMR spectra were superimposable on those of the (*S*)-(+)-isomer.

(*R*)-(−)-6-(2,3-Epoxypropoxy)-2(1*H*)-quinolinone (4a) A solution of KOH (1.42 g, 25.3 mmol) in H_2O (2.6 ml) was added to a stirred suspension of **3a** (1.5 g, 5.9 mmol) in 2-PrOH (20 ml) and H_2O (2.6 ml) at −10 °C. The reaction mixture was stirred for 2 h at the same temperature, then AcOH (1.1 ml, 17.5 mmol) was added and the whole was stirred for 1 h. The resulting precipitates were collected by filtration and washed with H_2O and EtOH to afford **4a** (0.86 g, 67.0%), mp 204—206 °C, $[\alpha]_D^{20}$ −7.3° (*c* = 1.27, *N*,*N*-dimethylformamide (DMF)). NMR (DMSO-d_6) δ: 2.70—2.73 (1H, m), 2.83—2.87 (1H, m), 3.32—3.50 (1H, m), 3.86 (1H, dd, *J* = 6.4, 11.2 Hz), 4.35 (1 H, dd, *J* = 2.6, 11.2 Hz), 6.49 (1H, d, *J* = 9.4 Hz), 7.19—7.24 (3H, m), 7.81 (1H, d, *J* = 9.4 Hz), 11.6 (1H, br s). IR (KBr): 1686, 1430, 1240, 1034, 868 cm^{-1}. *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.13; H, 5.04; N, 6.24.

(*S*)-(+)-6-(2,3-Epoxypropoxy)-2(1*H*)-quinolinone (4b) Compound **4b** (71.7%) was prepared by a procedure similar to that used for **4a**, mp 204—206 °C, $[\alpha]_D^{20}$ +7.2° (*c* = 1.27, DMF). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.18; H, 5.05; N, 6.30. The IR and NMR spectra were superimposable on those of the (*S*)-(+)-isomer.

(*R*)-(+)-6-[3-(3,4-Dimethoxybenzylamino)-2-hydroxypropoxy]-2(1*H*)-quinolinone [(*R*)-(+)-1] A mixture of **4a** (0.2 g, 0.92 mmol) and 3,4-dimethoxybenzylamine (2.2 g, 13.2 mmol) was stirred at 80 °C for 1 h, then cooled. Next, Et_2O was added, and the resulting precipitates were collected by filtration. Recrystallization from EtOH gave (*R*)-(+)-**1** (0.25 g, 70.6%) as colorless needles, mp 153—155 °C, $[\alpha]_D^{20}$ +9.5° (*c* = 0.44, MeOH). NMR (DMSO-d_6) δ: 2.29 (1H, br s), 2.58 (1H, dd, *J* = 11.8, 5.9 Hz), 2.66 (1H, dd, *J* = 4.8, 11.8 Hz), 3.65 (2H, br s), 3.72 (6H, s), 3.88—3.93 (2H, m), 3.99 (1H, dd, *J* = 7.0, 11.4 Hz), 4.97 (1 H, br s), 6.48 (1H, d, *J* = 9.6 Hz), 6.82 (1H, dd, *J* = 1.8, 8.8 Hz), 6.86 (1H, d, *J* = 8.8 Hz), 6.94 (1H, d, *J* = 1.8 Hz), 7.13 (1H, dd, *J* = 2.6, 8.8 Hz), 7.19 (1H, d, *J* = 2.6 Hz), 7.23 (1H, d, *J* = 8.8 Hz), 7.82 (1H, d, *J* = 9.6 Hz), 11.6 (1H, br s). IR (KBr): 1651, 1620, 1426, 1272, 1117 cm^{-1}. *Anal.* Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.38; H, 6.20; N, 7.28.

(*S*)-(−)-6-[3-(3,4-Dimethoxybenzylamino)-2-hydroxypropoxy]-2(1*H*)-quinolinone[(*S*)-(−)-1] Compound (*S*)-(−)-**1** (65.0%) was prepared by a procedure similar to that used for (*R*)-(+)-**1**. Colorless needles, mp 154—155 °C, $[\alpha]_D^{20}$ −9.4 °C (*c* = 0.51, MeOH). *Anal.* Calcd for

$C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.57; H, 6.29; N, 7.18. The IR and NMR spectra were superimposable on those of the (*R*)-isomer.

Determination of the Optical Purities of (*R*)-(+)- and (*S*)-(−)-1 The optical purities were determined as the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylisothiocyanate (GITC) derivatives according to the method of Sedman and Gal,[7,8] as follows. The chiral reagent GITC and other reagents were obtained from Wako (Osaka, Japan). Acetonitrile and tetrahydrofuran (THF) were of analytical reagent grade. The liquid chromatography was carried out on an HLC-803D pump equipped with an UV-8 model II detector (at a 254 nm fixed wavelength) (Tosoh, Tokyo, Japan), and a Yamamura (Tokyo, Japan) YMC-A312 ODS (5 μm, 150 mm × 6.0 mm i.d.) reversed-phase column, using an acetonitrile–water (35 : 65) mixture at a constant flow-rate of 1.5 ml/min. The chromatograms were recorded using a C-R3A electronic integrator (Shimadzu, Kyoto, Japan).

Each isomer (20 mg) was dissolved in THF (40 ml) containing Et_3N (0.1 ml). To a 50 μl aliquot of this solution was added 50 μl of THF solution containing 0.2% (w/v) GITC. The reaction mixture was allowed to stand at room temperature for 15 min, and a 2 μl aliquot of the mixture was injected into a chromatograph. The peaks of the diastereomeric GITC adducts of (±)-**1** showed base-line separation. The GITC adducts of the (*S*)- and (*R*)-form were eluted at 17 min and 20 min, respectively, and excess GITC appeared at 34 min. With each enantiomer, the peak of the other enantiomer was not detected, so the optical purity of each compound was concluded to be almost 100% ee.

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References and Notes

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