SYNTHESIS AND RESOLUTION OF THE OPTICAL ISOMERS OF THIENCYNONATE HYDROCHLORIDE

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ABSTRACT

Thiencynonate hydrochloride (*N*-methyl-9 α -(3-azabicyclo[3,3,1]nonanyl)-2'-cyclopentyl-2'-hydroxyl-2'-thienylacetate, **I**·HCl), a new muscarinic receptor antagonist, was synthesized and its enantiomers were obtained from the optical pure of demethylation product **II**. A convenient resolution method of demethylation product **II** has been developed with *N*-*p*-toluenesulfonylglutamic acid as the resolution reagent. The structures of **I** and **II** were elucidated by X-ray analysis.

Keywords: Thiencynonate hydrochloride, optical resolution, anticholinergic Drug

INTRODUCTION

Design, development, and marketing of new chiral drugs are now a major theme in the drug chirality research and industry.¹ In 1996, the FDA announced it would consider further incentives for developing single isomer drugs for their better pharmacokinetics prosperity, safety, and tolerability.² Our recent drug candidate: *N*-Methyl-9 α -(3-azabicyclo[3,3,1]nonanyl)-2'-cyclopentyl-2'-hydroxyl-2'-thienylacetate hydrochloride (Thiencynonate hydrochloride, **I**·HCl, Chart 1), is a potent selective M₁ antagonist. It is composed of a tertiary hydroxyl acid as a key component as like many of the muscarinic receptor antagonists. It exhibits classical antimuscarine side effects, such as dry mouth. The preliminary biology results suggest that the (*S*)-(-)-configuration of the tile compound display an improved therapeutic profile compared to its racemic counterpart. The optical resolution of racemates via diastereoisomeric salt formation is a common way for the preparation of optical isomers.^{3,4} We didn't found a suitable acid for the resolution of **I** due to the weak alkalescence of the tertiary N structure. In our efforts to have a production of the enantiopure, we synthesized the demethylation compound **II** to enhance the alkalescence. We found that inclusion crystallisation with *N*-*p*-toluenesulfonylglutamic acid(TSGA) as a chiral host is an effective method for the resolution of **II** with high enantiomeric excess.

(I) R = CH₃ Thiencynonate
(II) R = H

EXPERIMENTAL

General

All the reagents for syntheses were commercially available and used without further purification or purified by standard methods prior to use. Melting points were determined using a RY-1 apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C analyzer. ¹H-NMR spectra were measured in CDCl₃ using a multinuclear FT-NMR spectrometer ARX300 (Bruker). Mass spectra were obtained from Micromass ZabSpec and API3000 instruments. The enantiomeric excess of the title compound was determined by HPLC. Condition of HPLC: Hypersil BDS column and β -cyclodextrin as chiral mobile phase additive, methanol: acetonitrile: KH₂PO₄ (0.075mol·L⁻¹): H₂O = 25:2:60:18 as elute. α -Cyclopentyl- α -hydroxyl- α -thienylacetic acid was synthesized by addition of Grignard reagents to diethyl oxalate as described in the literature.⁸

Synthesis

9 α -(*N*-Methyl-3-azabicyclo[3,3,1]nonanyl)-2'-cyclopentyl-2'-hydroxyl-2'-thienylacetate **I**

Methyl α -cyclopentyl- α -hydroxyl- α -thienylacetate (2.6g, 11mmol) and 3-azabicyclo[3,3,1]nonan-9 α -ol (1.5g, 10mmol) were dissolved in anhydrous

n-heptane (100 mL), NaH(0.5g assay 80%) was added. The solution was reflux for 3 hours. The solvent was removed under reduced pressure; the residue was dissolved in ether (150 mL), washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to dryness. **I** was purified by flash-chromatography (chloroform/methanol, 9:1) and isolated as an oil (3.1g, 79%). Anal. Calcd for C₂₆H₂₉NO₃S: C, 66.08; H, 8.04; N, 3.85. Found: C, 66.14; H, 7.99; N, 3.91. ¹H NMR (CDCl₃) δ 7.24 (m, 1H, Ar-H), 7.12 (m, 1H, Ar-H), 7.08 (m, 1H, Ar-H), 4.81 (s, 1H, 1-OH), 4.12 (s, 1H, -OH), 3.01 (m, 3H), 2.55 (m, 1H), 2.25 (m, 2H), 2.15 (s, 3H, N-CH₃), 1.95 (m, 2H), 1.40-1.85 (m, 13H, cyclopentyl-H and nonanyl-H). MS (ESI): 364.2 (M+1)⁺.

9 α -(*N*-trichloroethylformyl-3-azabicyclo[3,3,1]nonanyl)-2'-cyclopentyl-2'-hydroxyl-2'-thienylacetate.

A mixture of **I** (3.6g, 10mmol) and 2,2,2-trichloroethylchloroformate(2.5 g, 12mmol) in 50mL anhydrous benzene was heated under reflux for 20 hours. After evaporation of the solvent and excessive 2,2,2-trichloroethylchloroformate, the residual oil was added to a solution of 50mL of 25%~28% NH₃·H₂O and 50mL of ether. The organic solution was washed with two 10mL portion of saturated brine, and dried over anhydrous magnesium sulfate. The solution evaporated under reduced pressure to give the product 4.7g (91% yield) as a yellow oil. ¹H NMR (CDCl₃) δ 7.21 (m, 1H, Ar-H), 7.08 (m, 1H, Ar-H), 7.03 (m, 1H, Ar-H), 4.79 (s, 1H, 1-OH), 4.64(s, 2H, -OCH₂CCl₃), 3.05 (s, 1H, -OH), 3.02 (m, 3H), 2.51 (m, 1H), 2.20 (m, 2H), 1.93 (m, 2H), 1.86 (m, 1H), 1.42-1.80 (m, 12H, cyclopentyl-H and nonanyl-H). MS (ESI): 524.2(M+1)⁺.

9 α -(3-azabicyclo[3,3,1]nonanyl)-2'-cyclopentyl-2'-hydroxyl-2'-thienylacetate. **rac-II**

A solution of the yellow oil product in 50ml glacial HOAc and 3.5g Zinc dust was stirred for 5 hours at room temperature. After removal of the Zinc by filtration, the filtrate was basified with concentrated NaOH and extracted with three 50-ml portions of ether. The solution evaporated under reduced pressure to give **rac-II** 2.8g (80% yield) of colorless solid, MS (ESI): 350.4(M+1)⁺. m.p. 131-133°. Anal. Calcd for C₁₉H₂₇NO₃S: C, 65.30; H, 7.79; N, 4.01. Found: C, 65.51; H, 7.61; N, 4.18. ¹H NMR (CDCl₃): 7.26(m, 1H, Ar-H), 7.15(m, 1H, Ar-H), 6.95(m, 1H, Ar-H), 4.97(s, 1H, 1-H), 4.12(br, 1H, -OH), 3.11(m, 5H), 2.86(m, 1H), 2.20(m, 1H), 2.00(m, 1H), 1.32-1.90(m, 14H, cyclopentyl-H and nonanyl-H).

Optical resolution of **rac-II**

A solution of **rac-II** (3.5g, 10mmol) and *L*-*N*-toluenesulfonylglutamic acid (TSGA) (3.0g, 10mmol) in anhydrous ethanol (150mL) was kept at 50° for 12 h. After being cooled to room temperature, a 1:1 inclusion complex (*S*)-(-)-**II**·*L*-TSGA was obtained as colorless crystals. Recrystallization of the salts from ethanol three times gave pure inclusion crystals. The inclusion complex was basified with 2 mol·L⁻¹ NaOH and extracted with ether (50mL $\times$ 3) and dried over anhydrous magnesium sulfate. The solution evaporated under reduced pressure to give optical pure (*S*)-(-)-**II**. 0.99g (56% yield). [α]_D²⁵ = -32.1°(c = 2, ethanol), 98.2% e.e. m.p. 132-133°. Anal. Calcd for C₁₉H₂₇NO₃S: C, 65.30; H, 7.79; N, 4.01. Found: C, 65.42; H, 7.73; N, 4.09.

The mother liquor was concentrated *in vacuo* and the residue was make alkaline with 2 mol·L⁻¹ NaOH. The ester was extract with ether (50mL $\times$ 3) and dried over anhydrous magnesium sulfate. After evaporation of the solvent, a solution of *D*-*N*-toluenesulfonylglutamic acid (4.0g, 13mmol) in anhydrous ethanol (100mL) was added and the salt (*R*)-(+)-**II**·*D*-TSGA formed was purified in same process as described above. (*R*)-(+)-**II** was obtained by basified the salt 1.05g (60% yield). [α]_D²⁵ = +32.5°(c = 2, ethanol), 99.1% e.e..

m.p. 132-133°. Anal. Calcd for $C_{19}H_{27}NO_3S$: C, 65.30; H, 7.79; N, 4.01. Found: C, 65.44; H, 7.82; N, 4.06.

(S)-(-)-I and *(R)-(+)-I*

(S)-(-)-I and *(R)-(+)-I* were synthesized by methylation of enantiopure **II**. *(R)-(+)-II* or *(S)-(-)-II* (0.97g, 2.8mmol) was dissolved in 30 mL anhydrous ethanol and 10 mL anhydrous Et_2O , 0.5mL CH_3I (3.2mmol) and 1 g K_2CO_3 were added. The mixture was stirred for 3 hours at room temperature. Additional 0.5 mL was added and then stirred for 24 hours. After removal of the K_2CO_3 by filtration, the filtrate was evaporated under reduced pressure and purified by flash-chromatography (chloroform/methanol, 9:1). *(S)-(-)-I* and *(R)-(+)-I* were isolated as an oil.

(S)-(-)-I [α]_D²⁰ = -7.3° (c = 0.5, $CHCl_3$), 99.1% e.e.. 1H NMR ($CDCl_3$): δ 7.24(m, 1H, Ar-H), 7.12(m, 1H, Ar-H), 6.98(m, 1H, Ar-H), 5.05(s, 1H, 1-H), 4.08(br, 1H, -OH), 3.82(m, 2H), 3.15(m, 2H), 2.93(s, 3H, N-CH₃), 2.92(m, 2H), 2.32(s, 1H), 2.21(s, 1H), 1.98(m, 2H), 1.42-1.86(m, 12H, cyclopentyl-H and nonanyl-H). MS (ESI): 364.2 (M+1)⁺.

(R)-(+)-I [α]_D²⁰ = +7.2° (c = 0.5, $CHCl_3$), 99.1% e.e.. 1H NMR ($CDCl_3$): δ 7.23 (m, 1H, Ar-H), 7.11 (m, 1H, Ar-H), 7.01 (m, 1H, Ar-H), 5.05 (s, 1H, 1-H), 4.09(br, 1H, -OH), 3.82 (m, 2H), 3.11 (m, 2H), 2.97 (s, 3H, N-CH₃), 2.94 (m, 2H), 2.31 (s, 1H), 2.18 (s, 1H), 1.92 (m, 2H), 1.40-1.85 (m, 12H, cyclopentyl-H and nonanyl-H). MS (ESI): 364.2 (M+1)⁺.

The oil was dissolved in Et_2O , 1M HCl/ Et_2O was dropped slowly. The mixture was stirring at room temperature for 1h. The precipitation was filtered and washed with cooled Et_2O , dried under vacuum. Thiencynonate hydrochloride was obtained as a white precipitate.

RESULTS AND DISCUSSION

Optical resolution of **I** was performed as outlined in Scheme 1. Racemate **I** can be conveniently synthesized by methyl α -cyclopentyl- α -hydroxyl- α -thienylacetate and 3-azabicyclo[3,3,1]nonan-9 α -ol. In order to demethylate of **I**, carbamate would be desirable. 2,2,2-trichloroethyl carbamate can be removed with zinc dust in glacial HOAc at room temperature.⁵ A 1:1 ratio of *rac-II* and *L-(-)-N-(p-methylphenylsulfonyl) glutamic acid(TSGA)* were mixed in the anhydrous ethanol at 50°C, then cooled and an inclusion complex of *(S)-(-)-II-L-TSGA* was separated out. The precipitated inclusion complex were recrystallized three times in the anhydrous ethanol. *(S)-(-)-II* was obtained through alkaline hydrolysis of the resolved acid. The mother liquor was concentrated and alkaline. The residue was added to a solution of *D-TSGA* and then *(R)-(+)-II* was obtained through alkaline hydrolysis of *(R)-(+)-II-D-TSGA* salts. *(S)-(+)-I* and *(R)-(-)-I* were synthesized by methylation of enantiopure **II** with CH_3I .

Scheme 1.

The colorless crystals of *(R)-(+)-II* and *(R)-(+)-I* suitable for X-ray analysis were obtained by recrystallization from dichloromethane solution. The X-ray ORTEP structure of the two compounds with atomic labelling is shown in Fig. 1. X-ray structure analytical data showed that the two compounds are similar composed of a 3-azabicyclo[3,3,1]nonane structure and a tertiary hydroxyl acid that adopted *R*-configuration. The bicyclic structure adopts a twin-chair conformation, this is the most favored conformation for the bicyclo[3,3,1]nonane ring system.^{6,7}

Figure 1. The crystal structures of *(R)-II* and *(R)-I*.

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