Optical Resolution of (±)-2-[4-(2-Oxycyclohexylidenemethyl)phenyl]propionic Acid

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The title compound showed potent anti-inflammatory and analgesic activities. For the determination of pharmacological activity differences between the optical isomers, we resolved the title compound via diastereomeric separation of the (−)-phenethyl amide derivatives and followed by amide bond cleavage with N₂O₄. The absolute configurations of the enantiomers were determined by comparison of the optical rotatory dispersion and circular dichroism spectra with those of known optically active 2-phenylpropionic acids.

Keywords anti-inflammatory; analgesic; optical rotatory dispersion; circular dichroism; optical resolution

Previously, we reported the synthesis of (±)-2-[4-(2-oxycyclopentylmethyl)phenyl]propionic acid (1) and (±)-2-[4-(2-oxycyclohexylidenemethyl)phenyl]propionic acid (2), which has good anti-inflammatory and analgesic activities. Among 2-arylpropionic acid derivatives having anti-inflammatory activity, considerable differences of pharmacological activities between their enantiomers are often observed. Thus, it is very important to synthesize the optically active compounds in order to investigate the pharmacological activities and metabolic pathway. Compound 1, which is on the market, has already been optically resolved and its absolute configuration determined.

In this paper, we describe the optical resolution and determination of the absolute configurations of the enantiomers of 2. In order to facilitate the separation of enantiomers, we tried to synthesize diastereomers of 1-phenylethylamide derivatives of 2 for optical resolution. Condensation of 2 with (−)-(1S)-1-phenylethylamine was carried out in the presence of triphenylphosphine and 2,2′-dipyridyl disulfide in dichloromethane at room temperature. High-pressure liquid chromatography (HPLC) of the reaction products showed two peaks due to two kinds of amides.

These were separated by preparative medium-pressure liquid chromatography (MPLC) (Si-60 Lobar column) to afford (−)-N-[((1S)-1-phenylmethyl)-(2R)-4-[2-oxycyclohexylidenemethyl]phenyl]propionamide (3) ([α]D₂₀ = −47.7°, mp 130-131 °C) and (−)-N-[((1S)-1-phenylmethyl)-(2S)-

[4-(2-oxycyclohexylidenemethyl)phenyl]propionamide (4) ([α]D₀²⁰ = 40.9°, mp 129-130 °C) as crystals. The structure of the amides, 3 and 4, were assigned on the basis of the following data and elemental analysis. The infrared (IR) spectra of 3 and 4 showed an amide band at 1650 and 1635 cm⁻¹ and a carbonyl absorption at 1680 and 1665 cm⁻¹, respectively. The nuclear magnetic resonance (NMR) spectrum of 3 exhibited two methyl proton peaks at 1.34 (doublet) and 1.48 ppm (doublet) and two methine proton peaks at 3.53 (quartet) and 5.09 ppm (quartet). Compound 4 had the corresponding methyl proton peaks at 1.36 and 1.50 ppm and methine proton peaks at 3.55 and 5.10 ppm. According to the literature, the less polar (−)-(1S)-phenylethylamide of a 2-arylpropionic acid generally has R-configuration at the 2-position of propionic acid and the more polar amide has S-configuration. Consequently, the less polar amide 3 may have R-configuration and the more polar 4 may have S-configuration.

Hydrolysis of 3 with concentrated HCl and AcOH af-

![Fig. 1. ORD Spectra of 2a and 2b](image)

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forded partially racemized compound 2a, because the benzyl methine proton has a relatively high $pK_a$ value. Therefore, cleavage of the amide bond of 3 and 4 was performed by diazotization with $N_2O_4$ followed by thermal decomposition in $CCl_4$ to afford the corresponding $-N-(1S)-1-Phenethylmethyl-(2R)-4-(2-oxocyclohexylidenemethyl)phloroglucinol [proponionic acid] (3) and $-N-(1S)-1-Phenethylmethyl-(2S)-4-(2-oxocyclohexylidenemethyl)phloroglucinol [proponionic acid] (4) A dichloromethane (10 mL) solution of 1.29 g of 2 was mixed with 1.1 g of 2,2-dipyrrolid disulfide, 1.31 g of triphenylphosphate and 0.6 g of (--)-1-(1S)-1-phenethylamine. The mixture reaction was kept at 0°C for 30 min and then concentrated under reduced pressure. The residue was chromatographed on silica gel (eluted with hexane-ethyl acetate (7:3)). The amide was further purified on a Si-60 Lobar column to give 0.8 g of 3 and 0.75 g of 4.  

3: mp 130-131 °C, [z]$_{D}^{20}$ 47.7° (c = 0.2% EtOH). IR (KBr): 3350, 1680, 1650 cm$^{-1}$. Anal. Calcd for C$_9$H$_{12}$NO$_2$: C, 79.74; H, 7.53; N, 3.88. Found: C, 79.49; H, 7.52; N, 3.73. $^1$H-NMR (CDCl$_3$) 6: 1.34 (3H, d, J = 7 Hz); 3.18 (3H, d, J = 7 Hz); 4.79 (2H, q, J = 7 Hz); 5.09 (1H, q, J = 7 Hz); 6.80 (1H(NH), br d, J = 8 Hz); 7.2-7.4 (10H, m).  

4: mp 129-130 °C, [z]$_{D}^{20}$ -40.9° (c = 0.2% EtOH). IR (KBr): 3300, 1665, 1633 cm$^{-1}$. Anal. Calcd for C$_9$H$_{12}$NO$_2$: C, 79.74; H, 7.53; N, 3.88. Found: C, 79.45; H, 7.54; N, 3.90. $^1$H-NMR (CDCl$_3$) 6: 1.36 (3H, d, J = 7 Hz); 1.50 (3H, d, J = 7 Hz); 1.6-2.1 (4H, m); 2.4-3.0 (4H, m); 3.53 (1H, q, J = 7 Hz); 5.10 (1H, q, J = 7 Hz); 6.80 (1H(NH), br d, J = 8 Hz); 7.2-7.4 (10H, m).  

$$\text{(-)-1(R)-2-[4-(2-Oxocyclohexylidenemethyl)phloroglucinol]}$$ propionic acid (2a)  

A stirred suspension of 2 g of sodium acetate in 12 mL of carbon tetrachloride (CCl$_4$) at $-78$ °C was treated with 4 mL of $N_2O_4$ (1 m $CCl_4$ solution). After 15 min, the stirred yellow suspension was treated dropwise with a solution of 680 mg of 3 in 1 mL of $CCl_4$ at 0°C and kept for 2 h. The reaction mixture was then diluted with 20 mL of water and extracted with ether. The solvent was evaporated off under reduced pressure and the residual oil was dissolved in 3 mL of $CCl_4$. This solution was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on l g of silica gel to afford 280 mg of the parent acid 1a. mp 101-103 °C; [z]$_{D}^{20}$ -51.4° (c = 0.18% MeOH). Anal. Calcd for C$_9$H$_{12}$O$_2$: C, 74.39; H, 7.02. Found: C, 74.30; H, 7.08.  

$$\text{(+)-1(S)-2-[4-(2-Oxocyclohexylidenemethyl)phloroglucinol]}$$ propionic acid (2b)  

Compound 4 (680 mg) was treated by the same procedure as described for 2a to give 500 mg of 2b. mp 101-103 °C; [z]$_{D}^{20}$ 51.4° (c = 0.18% MeOH). Anal. Calcd for C$_9$H$_{12}$O$_2$: C, 74.39; H, 7.02. Found: C, 74.21; H, 7.11.  

References  