An Improved Optical Resolution of 3-Acetylthio-2-methylpropionic Acid by Use of a New Chiral Amine, *N*-Isopropyl(phenylalaninol)

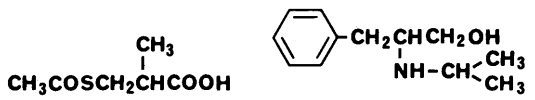
Tadahiro SAWAYAMA,* Masatoshi TSUKAMOTO, Takashi SASAGAWA, Shunsuke NARUTO, Jun-ichi MATSUMOTO and Hitoshi UNO

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki 33-94, Suita, Osaka 564, Japan. *Received October 4, 1988*

(*S*)-3-Acetylthio-2-methylpropionic acid was obtained in a good yield by an effective optical resolution with a newly synthesized chiral amine, (*S*)-*N*-isopropyl(phenylalaninol), which was readily derived from (*S*)-phenylalaninol, as a resolving agent.

Keywords angiotensin converting enzyme inhibitor; resolving agent; ternary phase diagram; eutectic composition

Studies[1,2] on angiotensin converting enzyme (ACE) inhibitors as agents for the treatment of hypertension and congestive heart failure are currently of great interest to medicinal chemists. (*S*)-3-Acetylthio-2-methylpropionic acid ((*S*)-**1**) is a common key intermediate in the preparation of a series of ACE inhibitors such as captopril,[3] pivopril[4] and alacepril,[5] which have a mercapto or a bioequivalent acylthio group and therefore, there has been much interest in the preparation of (*S*)-**1**, which has been obtained by several methods: optical resolutions[6] and utilization[7] of microorganisms. These methods, however, provide an optically impure product or insufficient yield, or involve a several-step synthesis.



1 **2**

Chart 1

As a part of our studies on ACE inhibitors, we investigated the optical resolution of compound **1**. We here present an efficient resolution of **1** by using a novel chiral amine, (*S*)-*N*-isopropyl(phenylalaninol) ((*S*)-**2**). Initially, the use[8] of several naturally occurring alkaloids and commercially available chiral amines as resolving agents proved to be ineffective. Therefore, we prepared many new chiral amines and among them selected the amine (*S*)-**2** as an agent. The chiral amine (*S*)-**2** was readily prepared by the reductive alkylation of (*S*)-phenylalaninol.[9] In an application of (*S*)-**2** to the resolution of **1**, we employed nonstoichiometric quantities (0.7 eq mol) of (*S*)-**2** to **1** in the first crystallization and obtained the partially resolved salt (80—86% enantiomeric excess (ee)) of (*S*)-**1** with (*S*)-**2** in *ca.* 58—62% yield based on the (*S*)-enantiomer. In order to find optimal conditions for the purification of the crude salt thus obtained, we determined the solubility ternary phase diagram[10] of the diastereomeric salts at 4 °C in ethyl acetate (Fig. 1). The eutectic composition (E) was found to consist of 95.7 wt% of the solvent, 1.63 wt% of the less soluble salt ((*S*)-**1**·(*S*)-**2**) and 2.67 wt% of the more soluble salt ((*R*)-**1**·(*S*)-**2**). On the basis of the eutectic location (E) on the diagram, the optimal amount of the solvent required for the purification of the salt (80% ee) and the yield were calculated[10] to be 78.5 wt% (of the whole system) and 85.6%, respectively. For the practical purification, however, 82.6 wt% amount of the solvent was employed to allow efficient

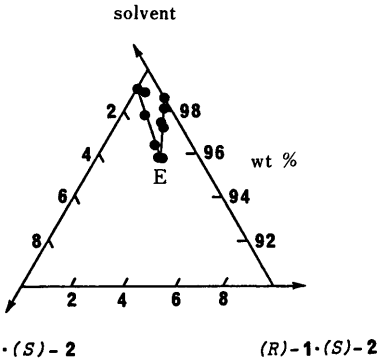


Fig. 1. Ternary Phase Diagram of Solubility of Diastereomeric Salts in Ethyl Acetate at 4 °C

Each point represents the solubility of a mixture of the less soluble salt and the more soluble salt. The solubility is expressed as weight percent of the whole mixture. The ratio of diastereomers of each point was determined from the observed rotation.

stirring; a mixture of the crude salt and ethyl acetate was stirred at 4 °C for 24 h, and pure salt with an optical purity of over 99% was obtained in *ca.* 78% yield. The overall yield of the pure salt was nearly 48% based on the (*S*)-enantiomer. Pure (*S*)-**1** was readily obtained by the decomposition of the pure salt with 10% sulfuric acid, and the agent (*S*)-**2** was nearly quantitatively recovered in a usual manner.

This procedure is simple and suitable for a laboratory-scale resolution of **1**. It could also be applicable to a large-scale production of (*S*)-**1**. Other applications of (*S*)-**2** as a resolving agent are now under investigation.

Experimental

Melting points were taken using a Yanaco micro melting point apparatus and are uncorrected. Proton nuclear magnetic sesonance (^{1}H-NMR) spectra were obtained using a Varian XL-300 MHz spectrometer and rotations at the Na-D line were observed using a Jasco DIP-4 digital polarimeter.

(*S*)-*N*-Isopropyl(phenylalaninol) ((*S*)-2) A solution of (*S*)-phenylalaninol (313 g) in acetone (230 ml) and ethanol (1250 ml) was stirred under a hydrogen atmosphere in the presence of platinum oxide (0.5 g) until absorption of hydrogen ceased. After removal of the catalyst, the filtrate was evaporated to dryness. Recrystallization of the residue from cyclohexane gave (*S*)-*N*-isopropyl(phenylalaninol); yield: 340 g (85%); mp 65—66 °C; $[\alpha]_D^{26}$ −5.4° (*c*=1.0, EtOH). *Anal.* Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.53; H, 9.70; N, 7.11. ^{1}H-NMR ($CDCl_3$/TMS): δ=0.98, 1.03 (3H each, 2d, *J*=6.2 each, $2CH_3$); 2.13 (2H, br s, NH+OH); 2.70 (1H, dd, *J*=7.3, 13.6, 1H of Ph-CH_2); 2.76 (1H, dd, *J*=6.4, 13.6, 1H of Ph-CH_2); 2.86 (1H, m, *J*=6.2, $CHMe_2$); 2.97 (1H, m, *J*=4.1, 5.9, 6.4, 7.3, C-CH-C); 3.24 (1H, dd, *J*=5.9, 10.5, 1H of CH_2-O); 3.55 (1H, dd, *J*=4.1, 10.5, 1H of CH_2-O); 7.1—7.35 (5H, m, arom.).

(*R*)-**2** was prepared according to the same procedure by using (*R*)-phenylalaninol: mp 64—66 °C; $[\alpha]_D^{26}$ +5.4° (c=1.0, EtOH).

Preparation of Standard Salt (*S*)-*N*-Isopropyl(phenylalaninolium) (*S*)-3-Acetylthio-2-methylpropionate ((*S*)-1·(*S*)-2) The standard salt was obtained by the following usual optical resolution method; purification was achieved by repeated recrystallization. A solution of (*RS*)-3-acetylthio-2-methylpropionic acid (**1**)[11] (95 g, 0.587 mol) and (*S*)-**2** (95 g, 0.491 mol) in ethyl acetate (1100 ml) was left overnight at 4 °C. The precipitated salt (109 g, mp 83—101 °C, $[\alpha]_D^{26}$ −8.7° (c=1.0, EtOH)) was collected by suction and recrystallized six times from ethyl acetate until there was no further change in optical rotation. Finally, 36 g (37%) of (*S*)-**1**·(*S*)-**2** was obtained; mp 103—104 °C; $[\alpha]_D^{26}$ −31.5° (c=1.0, EtOH). *Anal.* Calcd for $C_{18}H_{29}NO_4S$: C, 60.82; H, 8.22; N, 3.94; S, 9.02. Found: C, 60.54; H, 8.00; N, 3.98; S, 8.79.

Optical Resolution of (*RS*)-3-Acetylthio-2-methylpropionic Acid (1) A solution of **1** (720 g, 4.44 mol) and (*S*)-**2** (600 g, 3.11 mol) in ethyl acetate (6.9 l) was seeded with the pure salt ((*S*)-**1**·(*S*)-**2**, 2.0 g) and allowed to stand in a cold room (at 4 °C) for 2 d. The precipitated crude salt was collected by suction, washed with cold ethyl acetate and dried; yield: 485 g (61.5%, 80% ee); $[\alpha]_D^{26}$ −26.1° (c=1.0, EtOH).

A suspension of the crude salt (80% ee, 4.0 g, 17.4 wt%) in ethyl acetate (19.0 g, 82.6 wt%) was stirred in a cold room (at 4 °C) for 24 h without seeding. The precipitated pure salt was isolated by suction, washed with cold ethyl acetate (5 ml) and dried; yield: 3.13 g (>99% ee, 78.3%); mp 103—104 °C; $[\alpha]_D^{26}$ −30.9° (c=1.0, EtOH). *Anal.* Calcd for $C_{18}H_{29}NO_4S$: C, 60.82; H, 8.22; N, 3.94; S, 9.02. Found: C, 60.74; H, 8.32; N, 3.90; S, 8.91.

A solution of the pure salt (8.0 g) in water (30 ml) was acidified with 10% sulfuric acid (20 ml), and the mixture was extracted with ethyl acetate (3×40 ml). The extract was washed with brine (20 ml) and dried (Na_2SO_4). The solvent was evaporated off and the residue distilled to give (*S*)-**1** as a colorless oil; yield: 3.1 g (>99% e.e., 85%); bp 131—132 °C/2 mmHg; $[\alpha]_D^{26}$ −45.4° (c=1.0, EtOH) (Lit.[6a] $[\alpha]_D^{25}$ −41.2°(c=1.0, EtOH), Lit.[7] bp 115 °C/0.9 mmHg; $[\alpha]_D^{22}$ −48.55° (c=1.0, 95% EtOH)). *Anal.* Calcd for $C_6H_{10}O_3S$: C, 44.43; H, 6.21; S, 19.77. Found: C, 44.15; H, 6.45; S, 19.92.

The optical purity was determined based on capillary gas chromatographic (OV-17 (20 m×0.28 mm i.d.), 216 °C (isothermal), $\bar{\mu}$=20 cm/s) analysis of 1-(3-acetylthio-2-methylpropanoyl)-L-proline[3] derived from **1** and L-proline. The most highly purified (*S*)-**1** and its salt with (*S*)-**2** showed $[\alpha]_D^{26}$ −45.7° (c=1.0, EtOH) and $[\alpha]_D^{26}$ −31.5° (c=1.0, EtOH); mp 103—104 °C (ethyl acetate), respectively. Similarly, the pure (*R*)-**1** obtained by using (*R*)-**2** and its salt with (*S*)-**2** showed $[\alpha]_D^{26}$ +45.9° (c=1.0, EtOH) and $[\alpha]_D^{26}$ +24.0° (c=1.0, EtOH); mp 94—96 °C (ether/ethyl acetate), respectively.

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