

## Notes

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### Facile Preparation of optically Pure (3*S*)- and (3*R*)- 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid

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Optically pure (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**1**) was easily obtained by fractional crystallization of its benzyl ester (**2b**) *p*-toluenesulfonate, which was prepared from partially racemized **1** hydrochloride, followed by catalytic debenzylation. Similarly, (3*R*)-**1** was prepared by the same procedure. The degree of racemization during the Pictet-Spengler reaction using optically active phenylalanine was determined by <sup>1</sup>H-nuclear magnetic resonance (<sup>1</sup>H-NMR) spectroscopy of the corresponding methyl ester (**2a**), derived from the reaction product (**1**), in the presence of a chiral shift reagent.

**Keywords**—1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; benzyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate; phenylalanine; fractional crystallization; catalytic debenzylation; Pictet-Spengler reaction; racemization; chiral shift reagent

Optically active 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**1**) is a useful intermediate for the preparation of biologically active compounds.<sup>1)</sup> It has been reported that (3*S*)-**1**<sup>2)</sup> was prepared by means of the Pictet-Spengler reaction using L-phenylalanine and formalin in a similar way to that used for the preparation of racemic **1**.<sup>3)</sup> On the other hand, Hein *et al.* reported<sup>4)</sup> that partial racemization occurred under similar reaction conditions during the conversion of D-phenylalanine to (3*R*)-**1**, and that optically pure **1** was obtained by recrystallization of the crude product from aqueous ethanol until a constant rotation was observed.

In this paper, we report a facile preparation of optically pure **1** by fractional crystallization of its benzyl ester (**2b**) *p*-toluenesulfonate, followed by debenzylation.

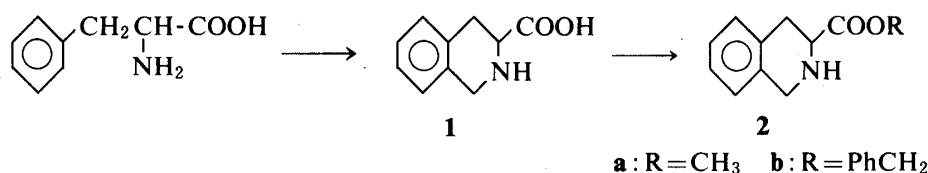


Chart 1

In order to confirm the degree of racemization during the Pictet-Spengler reaction, L- and DL-phenylalanine were each treated with formalin under the reported reaction condition<sup>3)</sup> to give **1** hydrochloride, which was converted to the corresponding methyl ester (**2a**) by reaction with thionyl chloride and methanol.

The <sup>1</sup>H-nuclear magnetic resonance (<sup>1</sup>H-NMR) spectra of the products **2a** (20 mg) in CDCl<sub>3</sub> showed a sharp singlet at 3.76 ppm attributable to the ester methyl protons. Among various chiral shift reagents tested, tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]-europium (III) [Eu(TFC)<sub>3</sub>] was found to be effective to detect racemization of **2a**, that is, after adding Eu(TFC)<sub>3</sub> (40 mg) to **2a** in CDCl<sub>3</sub>, the singlet signal was split into two peaks (5.14 ppm and 5.22 ppm), corresponding to the (*S*)-isomer and the (*R*)-isomer, respectively. In the case of the spectrum of **2a** derived from L-phenylalanine, the peak area at 5.14 ppm was about 5.2 times that at 5.22 ppm, while the spectrum of **2a** obtained from DL-phenylalanine showed

equal areas for the two peaks. Similarly, **2a** synthesized from D-phenylalanine showed a reverse peak area ratio as compared with that prepared from L-phenylalanine. From the above results, the degree of racemization during the cyclization reaction can be estimated to be about 32%.

Further, it was found that recrystallization of **1** was rather difficult due to its poor solubility in the solvent, and neither **1** hydrochloride nor **2a** hydrochloride could be effectively purified optically by recrystallization.

On the other hand, benzyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2b**) *p*-toluenesulfonate, prepared from **1** hydrochloride by reaction<sup>5)</sup> with benzyl alcohol and *p*-toluenesulfonic acid, was found to be a racemic mixture based on the solubilities and infrared (IR) spectra between racemic and optically active **2b** *p*-toluenesulfonates.

In practice, the fractional crystallization of partially racemized **2b** *p*-toluenesulfonate, prepared from L-phenylalanine, from aqueous methanol readily gave optically pure (3*S*)-**2b** *p*-toluenesulfonate,  $[\alpha]_D -61.0^\circ$ . The <sup>1</sup>H-NMR spectrum of (3*S*)-**2a**, derived from pure (3*S*)-**2b**, *p*-toluenesulfonate, showed a single peak for the ester methyl protons in the presence of Eu(TFC)<sub>3</sub>. Finally, catalytic debenzoylation of (3*S*)-**2b**, in aqueous ethanol containing acetic acid in the presence of palladium gave optically pure (3*S*)-**1**,  $[\alpha]_D -177.4^\circ$  (*c*=1, 1*N* NaOH).<sup>6)</sup> Similarly, optically pure (3*R*)-**1**, was obtained from D-phenylalanine by the same procedure as described for the preparation of (3*S*)-**1**.

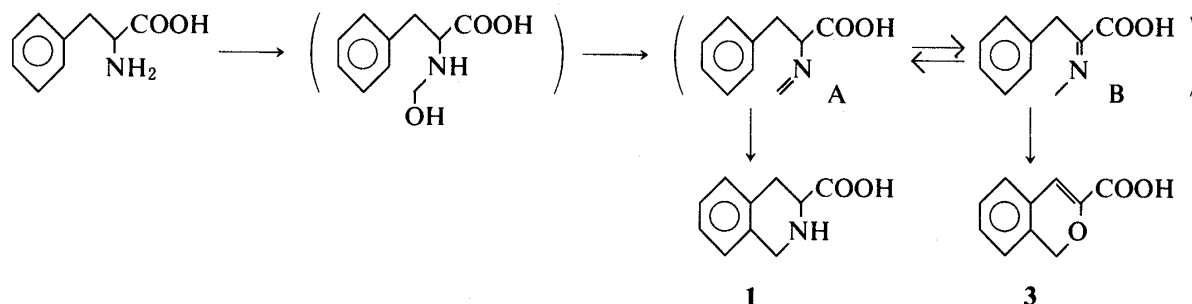


Chart 2

With regard to the mechanism of partial racemization during the Pictet-Spengler reaction with optically active phenylalanine, it is assumed that after coupling of the amino group with formalin, an equilibrium exists between dehydrated chiral azomethine A and achiral imine B, and then the desired product **1** is formed through partially racemized A as shown in Chart 2. This assumption is supported by the fact that a small amount of 1*H*-2-benzopyran-3-carboxylic acid (**3**) was isolated as a by-product from the mother liquor of **1**. The by-product (**3**) would be formed by hydrolysis of the imine B, followed by cyclization with formalin.

### Experimental

Melting points are uncorrected. IR spectra were obtained on a Shimadzu IR-27G spectrophotometer. <sup>1</sup>H-NMR spectra were recorded on a Hitachi R-20A instrument, using tetramethylsilane (TMS) as an internal Standard. Mass spectra (MS) were taken on a Hitachi R-60 mass spectrometer. Specific rotations were measured with a Perkin-Elmer 243 polarimeter.

**Methyl 1,2,3,4-Tetrahydroisoquinoline-3-carboxylate (2a)**—A mixture of L-phenylalanine (40 g), concentrated hydrochloric acid (310 ml) and 37% formalin (91 ml) was heated at 95–100°C with stirring for 4 h, then left to stand overnight at room temperature. The precipitate was collected by filtration. The filter cake was washed with cold water and acetone, then dried to yield crude (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**1**) hydrochloride as a crystalline powder (39 g, 75.4%). Thionyl chloride (10 g) was added dropwise to a suspension of the above obtained **1** hydrochloride (8 g) in MeOH (80 ml) with stirring at room temperature. The mixture was heated under reflux for 4 h and then concentrated *in vacuo*. The residue was washed with ether and dried to afford **2a** hydrochloride (7.8 g, 91.4%)<sup>7)</sup> as a colorless powder.

Optically pure (3*S*)-**2a** hydrochloride was prepared from (3*S*)-**1**, hydrochloride, described later, by the usual esterification procedure. mp 250–255°C (dec.) (from MeOH-Et<sub>2</sub>O).  $[\alpha]_D^{20} -104.1^\circ$  (*c*=1, MeOH).

IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 2600, 2500, 1740.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.16 (1H, s, NH), 2.75—3.05 (2H, m, Ar-CH<sub>2</sub>-CH), 3.72 (3H, s, COOCH<sub>3</sub>), 3.4—3.9 (1H, m, CH-N), 4.00 (2H, s, Ar-CH<sub>2</sub>-N), 6.8—7.1 (4H, m, aromatic H). *Anal.* Calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub>·HCl: C, 58.02; H, 6.20; Cl, 15.57; N, 6.15. Found: C, 57.96; H, 6.21; Cl, 15.21; N, 6.07.

**1*H*-2-Benzopyran-3-carboxylic Acid (3)**—The mother liquor and acetone washings of the above crude (3*S*)-**1** hydrochloride were evaporated to dryness. The residue was extracted with hot AcOEt and the extract was evaporated to dryness. The resulting residue was chromatographed on silica gel using CHCl<sub>3</sub>-AcOEt (9:1) as an eluent to give **3** (1.3 g, 3.0%), which was recrystallized from AcOEt to afford colorless scales. mp 196—199°C. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3300, 1725.  $^1\text{H-NMR}$  ( $d_6$  DMSO)  $\delta$ : 5.10, 5.20 (2H, Ar-CH<sub>2</sub>-O), 5.40 (1H, s, olefinic H), 7.3—7.8 (4H, m, aromatic H), 10.2—11.0 (1H, br s, COOH). MS  $m/e$ : 176 ( $\text{M}^+$ ). *Anal.* Calcd for C<sub>10</sub>H<sub>8</sub>O<sub>3</sub>: C, 68.18; H, 4.58. Found: C, 67.94; H, 4.79.

**Benzyl (3*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylate (2*b*)**—The title compound was prepared according to Hershenson's method<sup>5)</sup> as follows. A mixture of the above obtained crude (3*S*)-**1**, hydrochloride (25.0 g), benzyl alcohol (64 g), *p*-toluenesulfonic acid monohydrate (27 g) and benzene (300 ml) was heated under reflux for 5 h using a Dean-Stark trap. After removal of the solvent, ether was added to the residue and the resultant solid was collected by filtration. The solid was recrystallized twice from H<sub>2</sub>O-MeOH (2:1) to afford colorless needles of (3*S*)-**2b**, *p*-toluenesulfonate (32.0 g, 62.2%). mp 148—150°C.  $[\alpha]_D^{20}$  -61.2° ( $c=1$ , MeOH). IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 1735. *Anal.* Calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub>·C<sub>7</sub>H<sub>8</sub>O<sub>3</sub>S: C, 65.58; H, 5.73; N, 3.19; S, 7.30. Found: C, 65.56; H, 5.72; N, 3.17; S, 7.22.

(3*S*)-**2b** was obtained quantitatively from the *p*-toluenesulfonate by treatment with saturated NaHCO<sub>3</sub> and AcOEt, as a pale yellow oil.  $[\alpha]_D^{20}$  -88.3° ( $c=1.2$ , MeOH). IR  $\nu_{\text{max}}^{\text{film}}$   $\text{cm}^{-1}$ : 3320, 1730.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.19 (1H, s, NH), 2.9—3.1 (2H, m, Ar-CH<sub>2</sub>-CH), 3.6—3.9 (1H, m, CH-N), 4.06 (2H, s, Ar-CH<sub>2</sub>-N), 5.18 (2H, s, CH<sub>2</sub>-Ph), 7.0—7.15 (4H, m, aromatic H), 7.33 (5H, s, aromatic H). MS  $m/e$ : 267 ( $\text{M}^+$ ).

**(3*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (1)**—(3*S*)-**2b**, (3.4 g) was dissolved in a mixture of EtOH (40 ml), H<sub>2</sub>O (20 ml) and acetic acid (10 ml) and the solution was hydrogenated in the presence of 10% palladium on carbon (0.5 g) at room temperature and atmospheric pressure for 4 h. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo* to afford **1** as colorless scales (1.7 g, 75.4%). mp >280°C  $[\alpha]_D^{20}$  -177.4° ( $c=1$ , 1*N* NaOH).<sup>6)</sup>

**(3*R*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (1)**—The title compound was prepared from D-phenylalanine *via* crude (3*R*)-**1** hydrochloride and (3*R*)-**2b**, by the same procedure as described for the preparation of (3*S*)-**1**, mp >280°C  $[\alpha]_D^{20}$  -176.8° ( $c=1$ , 1*N* NaOH).

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#### References and Notes

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- 6) Ref. 4)  $[\alpha]_D^{20}$  -176.1° ( $c=1$ , 1.4*N* NaOH).
- 7) The optical purity of this compound was about 68% on the basis of NMR analysis using Eu(TFC)<sub>3</sub>.