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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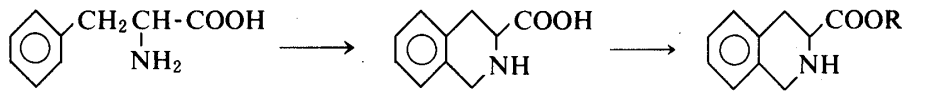
Optically pure (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**1**) was easily obtained by fractional crystallization of its benzyl ester (**2b**) *p*-toluenesulfonate, which was prepared from partially racemized **1** hydrochloride, followed by catalytic debenzylation. Similarly, (3*R*)-**1** was prepared by the same procedure. The degree of racemization during the Pictet-Spengler reaction using optically active phenylalanine was determined by ^{1}H-nuclear magnetic resonance (^{1}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.[1] It has been reported that (3*S*)-**1**[2] 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**.[3] On the other hand, Hein *et al.* reported[4] 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.



1 **2**

a: R=CH_3 **b**: R=$PhCH_2$

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[3] to give **1** hydrochloride, which was converted to the corresponding methyl ester (**2a**) by reaction with thionyl chloride and methanol.

The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra of the products **2a** (20 mg) in $CDCl_3$ 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)$_3$] was found to be effective to detect racemization of **2a**, that is, after adding Eu(TFC)$_3$ (40 mg) to **2a** in $CDCl_3$, 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

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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[5] 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°. The ^{1}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)$_3$. Finally, catalytic debenzylation 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° (*c*=1, 1N NaOH).[6] Similarly, optically pure (3*R*)-**1**, was obtained from D-phenylalanine by the same procedure as described for the preparation of (3*S*)-**1**.

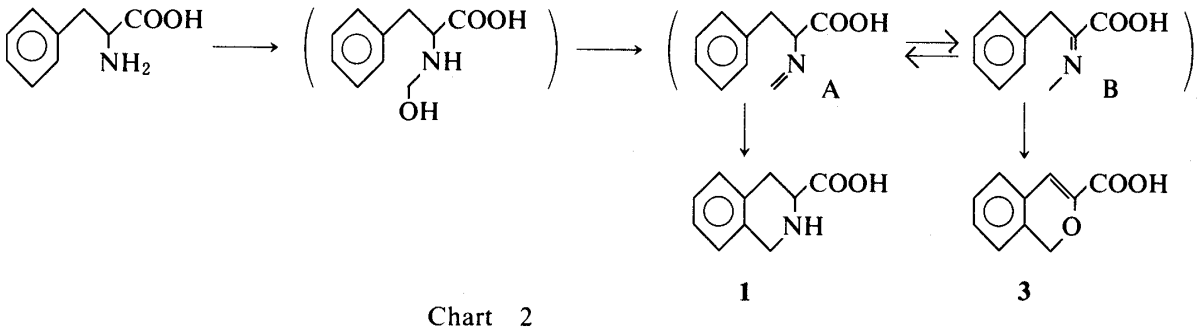

Chart 2

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. ^{1}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 yeild 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%)[7] 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_2O). $[\alpha]_D^{20}$ −104.1° (*c*=1, MeOH).

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IR ν_{max}^{Nujol} cm^{-1}: 2600, 2500, 1740. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (1H, s, NH), 2.75—3.05 (2H, m, Ar-CH_2-CH), 3.72 (3H, s, $COOCH_3$), 3.4—3.9 (1H, m, CH-N), 4.00 (2H, s, Ar-CH_2-N), 6.8—7.1 (4H, m, aromatic H). *Anal.* Calcd for $C_{11}H_{13}NO_2 \cdot HCl$: 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 $CHCl_3$–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 ν_{max}^{Nujol} cm^{-1}: 3300, 1725. ^{1}H-NMR (d_6 DMSO) δ: 5.10, 5.20 (2H, Ar-CH_2-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 (M^+). *Anal.* Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 67.94; H, 4.79.

Benzyl (3*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylate (2b)———The title compound was prepared according to Hershenson's method[5] 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_2O–MeOH (2:1) to afford colorless needles of (3*S*)-**2b**, *p*-toluenesulfonate (32.0 g, 62.2%). mp 148—150°C. $[\alpha]_D^{10}$ −61.2° (*c*=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1735. *Anal.* Calcd for $C_{17}H_{17}NO_2 \cdot C_7H_8O_3S$: 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 $NaHCO_3$ and AcOEt, as a pale yellow oil. $[\alpha]_D^{19}$ −88.3° (*c*=1.2, MeOH). IR ν_{max}^{film} cm^{-1}: 3320, 1730. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (1H, s, NH), 2.9—3.1 (2H, m, Ar-CH_2-CH), 3.6—3.9 (1H, m, CH-N), 4.06 (2H, s, Ar-CH_2-N), 5.18 (2H, s, CH_2-Ph), 7.0—7.15 (4H, m, aromatic H), 7.33 (5H, s, aromatic H). MS *m/e*: 267 (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_2O (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 $[\alpha]_D^{19}$ −177.4° (*c*=1, 1 N NaOH).[6]

(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 $[\alpha]_D^{21}$ −176.8° (*c*=1, 1 N NaOH).

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References and Notes

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5) F.M. Hershenson, *J. Org. Chem.*, **40**, 1260 (1975).
6) Ref. 4) $[\alpha]_D$ −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)$_3$.

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