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# Studies on Unusual Amino Acids and Their Peptides. X. The Convenient Synthesis of *t*-Leucine and the Optical Resolution of the *N*-Benzyloxycarbonyl Derivative[1)]

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**Synopsis.** *t*-Leucine has been conveniently prepared on a large scale from the phenylhydrazone of trimethylpyruvic acid, which was readily obtained as a precipitate from the oxidation of pinacolone. The *N*-benzyloxycarbonyl derivative of DL-*t*-leucine has been resolved with quinine and quinidine in ethanol.

In the course of investigation,[2)] it has been necessary to prepare optically active *t*-leucine on a large scale. For this purpose the route shown in Scheme was chosen.

$$Me_3C\text{-}CO\text{-}CH_3 \xrightarrow[OH^-]{KMnO_4} [Me_3C\text{-}CO\text{-}COOH] \xrightarrow{PhNHNH_2}$$

$$Me_3C\text{-}\underset{\underset{NNHPh}{\|}}{C}\text{-}COOH \xrightarrow{H_2/Pd\text{-}C} Me_3C\text{-}\underset{\underset{NH_2}{|}}{CH}\text{-}COOH$$

(I) (II)

Scheme.

Pinacolone has been oxidized with aqueous alkaline permanganate to trimethylpyruvic acid.[3)] This keto acid has been converted, without isolation, into the insoluble phenylhydrazone (I) and separated by filtration. Hydrogenation of I in the presence of palladium on carbon gave *t*-leucine (II) in good yield.

*N*-Z-DL-*t*-Leucine (III) has been resolved with quinine and quinidine in ethanol, and the optical purities of the resolved isomers confirmed by gas chromatographic analysis[4)] after conversion to the *N*-pivaloyl-*t*-leucyl-L-valine methyl ester.

## Experimental

All melting points are uncorrected. Optical rotations have been measured by Yanagimoto OR-10 and JASCO DIP-4 polarimeters.

*Phenylhydrazone of Trimethylpyruvic Acid (I).* Pinacolone (50 g) was oxidized with alkaline potassium permanganate (160 g) by Knoop's method.[3)] To the filtrate of the reaction mixture (*ca.* 5.5 l), after neutralization with HCl, was added phenylhydrazine (65 g) dissolved in acetic acid (250 ml) and the mixture allowed to stand at room temperature overnight. The resulting precipitates were separated by filtration, dried, and recrystallized from 70% ethanol, affording pale yellow needles (84 g, 76%) of mp 157—158 °C (lit,[5)] mp 157—158 °C).

*Hydrogenation of the Phenylhydrazone (I).* The phenylhydrazone (I) (100 g) was dissolved in a mixture of ethanol and water (510 ml EtOH+75 ml $H_2O$), and hydrogenated with 5% Pd–C (20 g) at 70 °C under an initial pressure of 50—140 kg/cm². The resulting solution was removed from the catalyst and evaporated to dryness under reduced pressure. The residue was dried sufficiently and washed repeatedly with dry benzene. The crude DL-*t*-leucine (II) (53.7 g; mp 248—251 °C (sublime)) was recrystallized from aqueous acetone; yield, 41.6 g (70%); mp 250—251 °C (sublime) (lit,[6,7)] mp 250 °C (sublime)).

*Optical Resolution of* N-*Z*-DL-*t*-*Leucine(III).* Thirty-eight mmol of III[8)] and quinine (or quinidine) were dissolved in hot ethanol (90 ml), and the precipitated white crystals recrystallized from ethanol four times. The purified salt was suspended in ethyl acetate, and shaken with 2 M HCl to remove the base, and subjected to the usual work-up. The optically active *t*-leucine was obtained by hydrogenation of the corresponding *N*-Z-derivative.

*N*-Z-D-*t*-Leucine quinine salt: mp 166—167 °C, $[\alpha]_D^{20}$ −106.5° (*c* 1.0, MeOH). Found: C, 69.46; H, 7.47; N, 7.12%. Calcd for $C_{34}H_{43}N_3O_6$: C, 69.24; H, 7.35; N, 7.13%.

*N*-Z-D-*t*-Leucine: syrup, $[\alpha]_D^{20}$ +5.9° (*c* 1.0, MeOH).

*N*-Z-D-*t*-Leucine dicyclohexylamine (DCHA) salt: mp 165.5—166 °C (from EtOH–$Et_2O$), $[\alpha]_D^{20}$ +8.5° (*c* 1.0, MeOH). Found: C, 69.90; H, 9.56; N, 6.04%. Calcd for $C_{26}H_{42}N_2O_4$: C, 69.92; H, 9.48; N, 6.27%.

D-*t*-Leucine: mp 250—252 °C (sublime), $[\alpha]_D^{21}$ +10.5° (*c* 1.0, $H_2O$), $[\alpha]_D^{20}$ −29.1° (*c* 1.0, AcOH) (lit,[9)] $[\alpha]_D^{20}$ +10.01° (*c* 5.19, $H_2O$) (*cf.* Refs. 3 and 10)). Found: C, 54.74; H, 9.87; N, 10.35%.

*N*-Z-L-*t*-Leucine quinidine salt: mp 134—136 °C (*ca.* 98 °C sinter), $[\alpha]_D^{20}$ +127.7° (*c* 1.0, MeOH).

*N*-Z-L-*t*-Leucine: syrup, $[\alpha]_D^{20}$ −6.0° (*c* 1.0, MeOH).

*N*-Z-L-*t*-Leucine DCHA salt: mp 166—166.5 °C (from EtOH–$Et_2O$), $[\alpha]_D^{20}$ −8.7° (*c* 1.0, MeOH) (lit,[11)] mp 165—168 °C, $[\alpha]_D$ −8.4° (*c* 0.59, MeOH)). Found: C, 69.79; H, 9.35; N, 5.98%.

L-*t*-Leucine: mp 250—252 °C (sublime), $[\alpha]_D^{21}$ −10.9° (*c* 1.0, $H_2O$), $[\alpha]_D^{26}$ +30.0° (*c* 1.0, AcOH) (lit, mp 250 °C (sublime),[12)] $[\alpha]_D^{28.5}$ −10.15° (*c* 4.63, $H_2O$)[9)] (*cf.* Refs. 3, 10, and 13), $[\alpha]_D^{25}$ +36.0° (*c* 2, AcOH)[3)]). Found: C, 54.77; H, 9.91; N, 10.35%.

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