PREPARATION OF L- AND D-3-PHENYLLACTIC ACIDS AND SOME OF THEIR DERIVATIVES

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In the course of the synthesis of depsipeptide analogs of biologically active peptides [1] the necessity arose for the preparation of L- and D-3-phenyllactic acids (L-I) and (D-I) and some of their derivatives. The reported methods for the resolution of DL-3-phenyllactic acid by the crystallization of its methyl ester [2] or of its salts with optically active bases such as brucine [3], morphine [4], or strychnine [5] give yields of not greater than 10-15% of the L- and D-isomers of 3-phenyllactic acid. In view of this we have developed a method of resolving racemic 3-phenyllactic acid with the aid of L- and D-threo-2-amino-1-p-nitrophenyl-1,3-propanediols (L-II) and (D-II), which we have previously used successfully in the preparation of optically active 2-hydroxy-3-methylbutyric acids [6]. By this method the optical isomers (L-I) and (D-I) were obtained in 55-58% yield.

We have also synthesized the L-3-phenyllactic acid derivatives (L-III)-(L-VI) and the dipeptide derivatives (L- and D-VII)-(L- and D-X) of general formula ROCH(CH_2C_6H_5)COOR', which can be used in the synthesis of linear depsipeptides containing L- and D-3-phenyllactic acids. Also, L-3-phenyllactic acid (L-I) and its derivatives (L-IV) and (L-V) were prepared from L-phenylalanine by the method proposed by Plattner and co-workers [7] for the preparation of t-butyl L-2-hydroxy-3-methylbutyrate from L-valine.

L-3-Phenyllactic Acid (L-I)

Preparation of the Salt (L-I . L-II). 20 g of DL-3-phenyllactic acid [8, 9] and 25.5 g of L-threo-2-amino-1-p-nitrophenyl-1,3-propanediol (L-II) [10] were dissolved at 40°C in 320 ml of water, and the solution was left for 16 h at 3-5°C. The precipitate was filtered off, washed with water, and dried at 40°C. We obtained the salt (L-I . L-II), which did not require further purification. Yield 19.6 g (86%); m.p. 134-135°C; [α]_D^20 + 24.0° (c 0.7, acetone). Found %: C 56.98; H 5.97; N 7.40. C_{18}H_{22}O_{7}N_{2}. Calculated %: C 57.15; H 5.82; N 7.41.

*BOC = benzyloxy carbonyl.
Isolation of L-3-Phenyllactic Acid (L-I). A suspension of 19.6 g of the salt (L-I-L-II) in 150 ml of water was acidified with concentrated HCl, and the solution was extracted exhaustively with ether. The extract was dried with MgSO₄ and vacuum-evaporated. The residue was dried in a vacuum desiccator over P₂O₅ and crystallized from benzene. The yield of (L-I) was 6.8 g (68%); m.p. 124-125°; [α]D²⁰ = -22.0° (c 0.8, water) (cf. [11]).

D-3-Phenyllactic Acid (D-I)

Preparation of the Salt (D-I-D-II). The aqueous solution obtained after the separation of the salt (L-I-L-II) was acidified with concentrated HCl and extracted exhaustively with ether. The extract was vacuum-evaporated, and the residue was dissolved at 40° in 120 ml of water. 13.2 g of D-threo-2-amino-1-p-nitrophenyl-1,3-propanediol (D-II) [10] was added to the solution, and the mixture was left overnight at 3-5°. The salt (D-I-D-II) was isolated as in the case of the salt (L-I-L-II). Yield 18.7 g (79.4%); m.p. 133-134°; [α]D²⁰ = -23.6° (c 0.7, acetone). Found %: C 56.90; H 5.76; N 7.46. C₁₃H₂₂O₇N₂. Calculated %: C 57.15; H 5.82; N 7.41.

Isolation of D-3-Phenyllactic Acid (D-I). The procedure was analogous to that used in the isolation of the acid (L-I). Yield 6.4 g (64%); m.p. 124-125°; [α]D²⁰ = +22.2° (c 0.8, water) (cf. [11]).

Benzyl L-3-Phenyllactate (L-III)

Hydrogen chloride was passed for 16 hours into a solution of 8.3 g of (L-I) in 40 ml of benzyl alcohol at between -5 and +5°, and the mixture was left for 16 h at 3-5°. Benzyl alcohol was distilled off at 110-120°, and the residue was vacuum-distilled. The yield of (L-III) was 11.5 g (90%); b.p. 136-137° (3·10⁻² mm); nD¹₈ 1.5610; d₄¹ 1.16; [α]D²⁰ = -13.3° (c 1 alcohol). Found %: C 74.68; H 6.13. C₁₆H₁₈O₃. Calculated %: C 75.00; H 6.25.

L-O-Acetyl-3-phenyllactic Acid (L-IV)

From L-3-Phenyllactic Acid. A solution of 28 g of (L-I) in 210 ml of acetic anhydride was heated to 100° and kept at that temperature for 2 h. Acetic anhydride was vacuum-distilled off. We obtained 35.6 g (about 100%) of (L-IVa) as an oil, which was chromatographically homogeneous. Mol.wt. 214 (found by titration); calculated 208.

From L-Phenylalanine. 18 g of L-phenylalanine was suspended in 150 ml of glacial acetic acid containing 9 g of fused sodium acetate, and at 15° 20 ml of isopentyl nitrite was added with stirring in the course of two hours. After 48 h the solution was vacuum-evaporated, 15 ml of concentrated HCl was added, and the precipitated oil was extracted with ether. The ether extract was shaken repeatedly with saturated KHCO₃ solution, and the aqueous solution was acidified with concentrated HCl and extracted with ether. The extract was dried with MgSO₄ and vacuum-evaporated. We obtained 15.8 g (70%) of (L-IVb) in the form of an oil. Mol.wt. 215 (found by titration); calculated 208.

The L-O-acetyl-3-phenyllactic acid obtained by both methods was used in the next stage without purification.

t-Butyl L-O-Acetyl-3-phenyllactate (L-V)

35.7 g of (L-IVa) was dissolved in 370 ml of methylene chloride containing 2.5 ml of concentrated H₂SO₄, and the solution was saturated at 0° with isobutene until the volume had doubled and then left at room temperature for 48 h. Air was blown through the solution, to which 150 ml of ether was added, and the ether solution was washed with 10% Na₂CO₃ solution and water; it was dried with MgSO₄. Solvent was vacuum-evaporated. We obtained 39.46 g (88%) of the ester (L-V) in the form of a colorless chromatographically homogeneous oil (nD²⁰ 1.4790) which gradually crystallized; m.p. 37-38°. An analytical sample had m.p. 42-43° (petroleum ether); [α]D¹⁸ = -13° (c 1.5, alcohol). Found %: C 68.14; H 7.80. C₁₅H₂₆O₄. Calculated %: C 68.13; H 7.63.

t-Butyl L-3-Phenyllactate (L-VI)

9 ml of 2 N NaOH was added with stirring to a suspension of 7.3 g of (L-V)† in 10 ml of 70% methanol cooled to 0°, stirring was continued further for three hours at room temperature, 5 ml of water was added, *When necessary the substance was vacuum-distilled with collection of the fraction of b.p. 88-92° (7.10⁻² mm).
† For the hydrolysis it is best to use the uncrystallized substance.