Preparation of DL-β-Leucine. Amino Acids, XV*

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By application of the Arndt-Eistert reaction to the diazoketone of N-phthaloyl-DL-valine, racemic β-leucine has been prepared and tested against Staphylococcus aureus, B. pyocyaneus, E. coli and Enterococcus.

It has been shown that β-amino acids can easily be prepared by the Arndt-Eistert-homologisation of α-amino acids, the free amino group being protected by the phthaloyl group (1-6). Following this method (-)-β-leucine was prepared recently from N-phthaloyl-D-valine7. In this paper the preparation of racemic β-leucine (β-amino-γ-methyl-valeric acid, homovaline) [I] is reported, with N-phthaloyl-DL-valine [II] as starting material. β-Leucine was earlier prepared by hydrolizing 4-isopropyl-dihydouracil with hydrochloric acid8.

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{CH} \quad \text{CH} \quad \text{CH}_2\text{COOH} \\
\text{II} \\
\text{H}_3\text{C} \\
\text{CH} \quad \text{CH} \quad \text{R}^2 \\
\text{H}_3\text{C} \\
\text{CH} \quad \text{R}^1 \\
\text{R}^1 = \text{N(CO)}_2\text{C}_6\text{H}_4 \\
\text{R}^2 = \text{COOH} \\
\text{III} \text{ R}^2 = \text{COCl} \\
\text{IV} \text{ R}^2 = \text{COCHN}_2 \\
\text{V} \text{ R}^2 = \text{COCH}_2\text{Br} \\
\text{VI} \text{ R}^2 = \text{CH}_3\text{COOCH}_3 \\
\text{VII} \text{ R}^2 = \text{CH}_3\text{COOH}
\end{array}
\]

N-Phthaloyl-DL-valine [II], reported earlier by Billman and Hartung9, was prepared by a slightly modified3-9 general method of Reese11, described by Minard and Fox12. The acid chloride [III] was prepared by the action of thionyl chloride on N-phthaloyl-DL-valine [II]. Contrary to Foye and Hofferren13 — who were unable to obtain the chloride in a crystalline form — the chloride is a crystalline solid which readily crystallizes from thionyl chloride (light petroleum ether) sublimed in vacuo it melts at 87-89°. The chloride [III] was converted to the diazoketone [IV], which on treatment with hydrobromic


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Acid\textsuperscript{14-16} gave the corresponding bromoketone [V]. Wolff-rearrangement of the diazoketone [IV] gave the methyl ester of \( N \)-phthaloyl-DL-homovaline [VI], which was partially hydrolyzed to the corresponding phthalimido-acid [VII]. DL-\( \beta \)-leucine [I] was obtained on acid hydrolysis of the phthalimido homoaacid methyl ester [VI].

Of the compounds described in the present paper \( N \)-phthaloyl-DL-\( \beta \)-leucine [VII], DL-\( \beta \)-leucine [I] and the earlier reported (-)-\( \beta \)-leucine\textsuperscript{7} were tested on \textit{Bacillus coli, Bacillus pyocyaneus, Enterococcus} and \textit{Staphylococcus aureus} at a dilution of 10 mg./ml. Preliminary tests showed no antibacterial activity of \( N \)-phthaloyl-DL-\( \beta \)-leucine [VII] when tested as sodium salt. While (-)-\( \beta \)-leucine was found to be inactive, racemic \( \beta \)-leucine exhibited a marked growth-stimulating effect. Since (-)-\( \beta \)-leucine has apparently D-configuration\textsuperscript{17}, the growth-stimulating activity of the racemate is probably due to the metabolizability of the yet undescribed L-isomer.

**EXPERIMENTAL**

\textbf{\( N \)-Phthaloyl-DL-valine [II]}

Prepared by heating DL-valine\textsuperscript{18} (23.4 g., 0.2 mole) and phthalanhydride (29.6 g., 0.2 mole) at 140-145\textdegree C for one hour, dissolving the warm clear melt in abs. ethanol (40 ml.) and precipitating the phthalimido-acid by pouring the ethanolic solution into water (230 ml.) with shaking and cooling. Yield, 92-97\%. Recrystallized from carbon tetrachloride/petroleum ether the product melted at 104\textdegree C. The earlier reported melting points were 101.5-102\textdegree (uncorr.)\textsuperscript{9} and 102-103\textdegree (uncorr.)\textsuperscript{12}, respectively.

\textbf{DL-2-Methyl-2-phthalimido-butanoyl chloride [III]}

\( N \)-Phthaloyl-DL-valine [II] (24.7 g., 0.1 mole) was dissolved in thionyl chloride (77.3 g., 0.65 mole). After standing overnight at room temperature the excess of thionyl chloride was evaporated under reduced pressure and the chloride precipitated as a crystalline solid by the addition of light petroleum ether. Yield, 92\%. Recrystallized from thionyl chloride/petroleum ether, and sublimed at 100\textdegree C, 0.1 mm. the product melted at 87-89\textdegree.

\textbf{Anal.}\n
11.803 mg subst.: 25.320 mg CO\textsubscript{2}, 4.735 mg H\textsubscript{2}O

\textbf{DL-1-Diazo-4-methyl-3-phthalimido-pentan-2-one [IV]}

The acid chloride [III] (23.8 g., 0.09 mole) was dissolved in ether (125 ml.) and gradually added to an ethereal solution (1000 ml.) of diazomethane (obtained from 70.0 g., 0.68 mole of nitroso-methyl-urea). After standing overnight the solution was evaporated to dryness under reduced pressure giving yellow crystals of the diazo-ketone (24.0 g., 98.5\%), which after recrystallization from carbon tetrachloride/petroleum ether melted at 76.5\textdegree.

\textbf{Anal.}\n
9.390 mg subst.: 21.29 mg CO\textsubscript{2}, 4.09 mg H\textsubscript{2}O

\textbf{DL-1-Bromo-4-methyl-3-phthalimido-pentan-2-one [V]}

To a solution of the diazoketone [IV] (15.3 g., 0.056 mole) in glacial acetic acid (75 ml.), 48\% hydrobromic acid (14.5 ml.) was gradually added with stirring and

* The melting points were determined with a Kofler micro melting point apparatus.
cooling. After standing for one hour at room temperature the bromoketone (15.4 g., 84.1%) was precipitated by the addition of water (820 ml.). Recrystallization from carbon tetrachloride/petroleum ether gave pale yellow prisms of the bromoketone melting at 83-86°C.

Anal. 9.930 mg. subst.: 19.063 mg. CO₂, 3.818 mg. H₂O
C₁₅H₁₁BrNO₃ (324.18) calc’d: C 51.88; H 4.35%
found: C 52.39; H 4.30%

Methyl DL-4-methyl-3-phthalimido-pentanoate [VI]

A freshly prepared methanolic suspension of silver oxide (obtained from 3.0 g. of silver nitrate) was gradually added to a boiling solution of the diazoketone [IV] (41.0 g., 0.15 mole) in methanol (73 ml.) until the evolution of nitrogen ceased (3 hours). After refluxing for additional four hours, charcoal was added, the suspension filtered and the filtrate evaporated to dryness under reduced pressure giving the crystalline homoester [VI] (35.5 g., 86%), which after recrystallization from carbon tetrachloride/petroleum ether melted at 79°C.

Anal. 8.760 mg. subst.: 21.07 mg. CO₂, 4.88 mg. H₂O
C₁₅H₁₁NO₄ (275.30) calc’d: C 65.43; H 6.23%
found: C 65.64; H 6.23%

DL-4-Methyl-3-phthalimido-pentanoic acid [VII]

A mixture of the homo-ester [VI] (2.75 g., 0.011 mole), 48% hydrobromic acid (41.5 ml.) and glacial acetic acid (8.7 ml.) was warmed at 40-50°C for 2.5 hours. The cooled clear solution was poured into water (35 ml.) and the separated oil again suspended in water (50 ml.). The water layer was decanted and the residue dissolved in a few drops of absolute ethanol. On standing in a dessicator the oily phthalimido-acid [VII] solidified (1.9 g, 72.8%), which after recrystallization from carbon tetrachloride/petroleum ether, it melted at 88-90°C.

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