CROATICA CHEMICA ACTA 28 (1956) 303

\( \text{L-} \beta\text{-Methionine and Related Compounds*} \)

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Received December 4, 1956

Work on optically active \( \beta \)-amino acids* has been continued in this Laboratory and a description is now given of the preparation of L-\( \beta \)-methionine (I) and of L-\( \beta \)-homodjenkolic acid (II).

\[
\begin{align*}
\text{I. } & \text{R = CH}_3 \\
\text{II. } & \text{R = C}_6\text{H}_5\text{CH}_2
\end{align*}
\]

The only difference between L-\( \beta \)-methionine and natural methionine is the position of the amino groups. The biological importance of methionine\(^1\) is well-known. It is an indispensable amino acid for the growing rat, and is important in in vivo transmethylations.\(^2\)

It has been shown that the formation of creatine from methionine and guanidinoacetic acid involves two different enzymatic reactions. In the first reaction an "active methionine" is formed from L-methionine and adenosine-triphosphate in the presence of the methionine activating enzymes\(^3\)\(^,\)\(^4\), magnesium ion, and glutathione; in the second reaction which is catalysed by guanidino-acetic acid methylpherase,\(^4\) the methyl group is transferred from active methionine to guanidino-acetic acid. Active methionine has already been isolated.\(^5\) It is believed to be a sulphonium compound in which the sulphur atom of methionine is linked to the 5' -carbon of adenosine.

Many questions remain unsolved concerning, inter alia, the specificity of different enzymatic reactions in which L-methionine is involved. In connection with this the synthesis of L-\( \beta \)-methionine could be of considerable interest. DL-\( \beta \)-Methionine was recently prepared by addition of ammonia to \( \gamma \)-methylmercaptoeptofonic acid.\(^7\)

A few years ago\(^8\) the Arndt-Eistert reaction was applied to optically impure S-benzyl-N-phthaloyl-L-cysteine ([\( \alpha \)]\( D \) = -82\(^\circ\)) and partly racemic S-benzyl-\( \beta \)-homocysteine (Ia) was obtained, a starting material for the synthesis of sulphur-containing \( \beta \)-amino acids.\(^9\).


** Abstracted in part from the Doctor's thesis presented by D. Fleš to the Faculty of Science, University of Zagreb, in October 1952.
A description has recently been given of optically pure \( S \)-benzyl-\( N \)-phthaloyl-\( L \)-cysteine \([\alpha]_D -167^\circ\)\(^{10}\) which, after the usual reaction stages of the Arndt- Einstert synthesis, afforded optically pure \( S \)-benzyl-\( \beta \)-homocysteine \((\text{Ia}, [\alpha]_D -57^\circ)\).\(^{11}\) \( L \)-\( \beta \)-Methionine and \( L \)-\( \beta \)-homodjenkolic acid were prepared in a similar manner as \( L \)-methionine; the former was obtained from Ia and methyl iodide in liquid ammonia following Patterson and du Vigneaud,\(^12\) the latter from Ia and dichloromethane.\(^13\)

The Wolff rearrangement of the diazoketones used in the Arndt-Eistert procedure is known to proceed with retention of configuration when the rearrangement occurs at an asymmetrical centre;\(^14\) therefore \( \beta \)-methionine \((\text{I})\) and \( \beta \)-homodjenkolic acid \((\text{II})\) were presumed to be of the \( L \)-configuration.\(^a\) This assumption has recently been confirmed\(^15\) by direct chemical correlation of the configurations of \( \beta \)-amino acids with \( \alpha \)-amino acids.

**Experimental**

All melting points are uncorrected.

\( L \)-\( \beta \)-Methionine (I)

To a solution of \( S \)-benzyl-\( L \)-\( \beta \)-homocysteine\(^{11}\) \((\text{Ia}, [\alpha]_D -57^\circ, 0.9 \text{ g}, 0.004 \text{ mole})\) in anhydrous liquid ammonia\(^2\) (50 ml.) sodium was gradually added (0.3 g., 0.013 mole) until the blue colour of the reaction mixture remained permanent. Methyl iodide was added (0.63 g., 0.0044 mole); a sample of the reaction mixture did not show a positive sulfhydryl test with sodium nitroprusside. Ammonium chloride (530 mg., 0.01 mole) was added and the ammonia evaporated overnight. The last traces of ammonia were removed in \( \textit{vacuo} \) and the residue dissolved in water (15 ml.), treated with charcoal, diluted with water (600 ml.) and passed through a column of Amberlite IR-100 (300 g., 40–50 mesh) at a flow rate of 300 ml./hr. After washing the column until a negative reaction on halogen ions, \( \beta \)-methionine was obtained by elution of the column with 1% aqueous pyridine (4000 ml.); after evaporating the eluate under reduced pressure, the crude \( \beta \)-methionine was obtained (yield 0.50 g., 84%).

To a solution of crude oily \( L \)-\( \beta \)-methionine (0.50 g.) in 96% ethanol (10 ml.) acetone (5 ml.) was added and the mixture left overnight at 0°. Crystallization occurred. After recrystallization from ethanol-acetone \((2 : 1)\) colourless prisms of \( L \)-\( \beta \)-methionine with the constant m. p. 166–167° (decomp.), and \([\alpha]_D^{20} -23^\circ \pm 1^\circ \) \((c, 1.535 \text{ in water})\) were obtained. The DL compound showed the m. p. 196°.\(^7\)

Paper chromatography on Whatman No. 1 filter paper at 23° and with \( 1 \)-butanol–glacial acetic acid–water \((10 : 3 : 8)\) as mobile phase gave a violet spot with ninhydrin, \( R_f 0.33 \).

**Anal.** 11.95 mg. subst.: 17.68 mg. \( \text{CO}_2 \), 7.95 mg. \( \text{H}_2\text{O} \)

\( C_5\text{H}_{11}\text{O}_2\text{NS} \) (149.21) calc’d.: C 40.24; H 7.43\% found: C 40.39; H 7.44\%

\( L \)-\( \beta \)-Homodjenkolic Acid (II)

A solution of \( S \)-benzyl-\( L \)-\( \beta \)-homocysteine\(^{11}\) \((\text{Ia}, [\alpha]_D -57^\circ, 0.9 \text{ g}, 0.004 \text{ mole})\) in liquid ammonia (30 ml.) was reduced with sodium \((0.23 \text{ g}, 0.01 \text{ mole})\) and dichloromethane \((0.5 \text{ ml}, 0.008 \text{ mole})\) added\(^13\) with vigorous stirring. After half an hour, the sulfhydryl test with sodium nitroprusside was negative. Ammonium chloride \((0.59 \text{ g})\) was added, and the mixture left standing overnight. The dry residue was dissolved in water (750 ml.) and passed through a column containing Amberlite IR-100 under the same conditions as described for the isolation of I. \( L \)-\( \beta \)-Homodjenkolic acid was obtained from the column with aqueous pyridine. The first

\(^a\) In this paper \( L \) is used in an extension of the convention for \( \alpha \)-amino acids to \( \beta \)-amino acids.
fraction (4000 ml., 10/\text{o} aqueous pyridine), after evaporation to dryness in vacuo (bath temp. below 35\(^\circ\)) yielded crude oily L-\(\beta\)-homodjenkolic acid (0.38 g., 68\%/\text{o}) with \([\alpha]_D^{25} = -116^\circ \pm 2^\circ\) (c, 0.75 in water). The second fraction (0.51 g.) contained small quantities of II, and had \([\alpha]_D^{24} = -21^\circ\). The third fraction contained no II.

Three recrystallizations of the first fraction from aqueous ethanol (1:1) gave "colourless needles of the pure compound showing the m.p. 213\(^\circ\) (decomp.) and \([\alpha]_D^{25} = -110^\circ \pm 2^\circ\) (c, 0.71 in water).

Paper chromatography on Whatman No. 1 filter paper at 23\(^\circ\), with phenol-water as mobile phase gave a violet spot with ninhydrin, \(R_f 0.59\). L-\(\beta\)-Homodjenkolic acid contaminated with inorganic salts gave much higher \(R_f\) values.

Anal. 8.16 mg. subst.: 11.46 mg. \(\text{CO}_2, 4.65\) mg. \(\text{H}_2\text{O}
\text{C}_9\text{H}_{15}\text{O}_4\text{N}_2\text{S}_2\) (2S2.37)
calc'd.: C 38.28; H 6.42\%/\text{o}
found: C 38.33; H 6.38\%/\text{o}

Thanks are due to Mrs. Z. Stefanac for the micro-analyses.

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14. cf. e.g. J. F. Lane, J. Willenz, A. Weissberger and E. S. Wallis, J. Org. Chem. 5 (1940) 276.

IZVOD

L-\(\beta\)-Metionin i srodni spojevi

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Opisuje se sinteza L-\(\beta\)-metionina (I), t. t. 166—167\(^\circ\), \([\alpha]_D^{20} = -23^\circ\) (c, 1.535 u vodi) i L-\(\beta\)-homodjenkolne kiseline (II), t. t. 213\(^\circ\), \([\alpha]_D^{22} = -110^\circ\) (c, 0.71 u vodi), polazeći od S-benzil-L-\(\beta\)-homocisteina.