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L-β-Methionine and Related Compounds*

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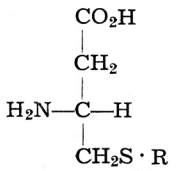
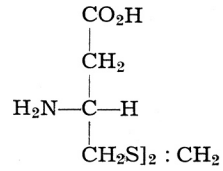
Work on optically active β-amino acids* has been continued in this Laboratory and a description is now given of the preparation of L-β-methionine (I) and of L-β-homodjenkolic acid (II).



I. $R = CH_3$

Ia. $R = C_6H_5CH_2$



II

The only difference between L-β-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[3,5], 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-β-methionine could be of considerable interest. DL-β-Methionine was recently prepared by addition of ammonia to γ-methylmercaptocrotonic 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°) and partly racemic *S*-benzyl-β-homocysteine (Ia) was obtained, a starting material for the synthesis of sulphur-containing β-amino acids.[9].

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A description has recently been given of optically pure *S*-benzyl-*N*-phthaloyl-L-cysteine $[\alpha]_D$ —167°)[10] which, after the usual reaction stages of the Arndt- Einstert synthesis, afforded optically pure *S*-benzyl-L-β-homocysteine (Ia, $[\alpha]_D$ —57°).[11] L-β-Methionine and L-β-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 β-methionine (I) and β-homodjenkolic acid (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 β-amino acids with α-amino acids.

EXPERIMENTAL

All melting points are uncorrected.

L-β-*Methionine* (I)

To a solution of *S*-benzyl-L-β-homocysteine[11] (Ia, $[\alpha]_D$—57°, 0.9 g., 0.004 mole) in anhydrous liquid ammonia[12] (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 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, β-methionine was obtained by elution of the column with 1% aqueous pyridine (4000 ml.); after evaporating the eluate under reduced pressure, the crude β-methionine was obtained (yield 0.50 g., 84%).

To a solution of crude oily L-β-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-β-*methionine* with the constant m. p. 166—167° (decomp.), and $[\alpha]_D^{20}$ —23° ± 1° (c, 1.535 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. CO_2, 7.95 mg. H_2O
$C_5H_{11}O_2NS$ (149.21) calc'd.: C 40.24; H 7.43%
found: C 40.39; H 7.44%

L-β-*Homodjenkolic Acid* (II)

A solution of *S*-benzyl-L-β-homocysteine[11] (Ia, $[\alpha]_D$ —57°, 0.9 g., 0.004 mole) in liquid ammonia (30 ml.) was reduced with sodium (0.23 g., 0.01 mole) and dichloromethane (0.5 ml., 0.008 mole) added[13] with vigorous stirring. After half an hour, the sulfhydryl test with sodium nitroprusside was negative. Ammonium chloride (0.59 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-β-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 α-amino acids to β-amino acids.

fraction (4000 ml., 1% aqueous pyridine), after evaporation to dryness *in vacuo* (bath temp. below 35°) yielded crude oily L-β-homodjenkolic acid (0.38 g., 68%) with $[\alpha]_D^{25}$ —116° ± 2° (c, 0.75 in water). The second fraction (0.51 g.) contained small quantities of II, and had $[\alpha]_D^{24}$ —21°. 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° (decomp.) and $[\alpha]_D^{25}$ —110° ± 2° (c, 0.71 in water).

Paper chromatography on Whatman No. 1 filter paper at 23°, with phenol-water as mobile phase gave a violet spot with ninhydrin, R_f 0.59. L-β-Homodjenkolic acid contaminated with inorganic salts gave much higher R_f values.[16]

Anal. 8.16 mg. subst.: 11.46 mg. CO_2, 4.65 mg. H_2O
$C_9H_{18}O_4N_2S_2$ (282.37) calc'd.: C 38.28; H 6.42%
found: C 38.33; H 6.38%

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IZVOD

L-β-Metionin i srodni spojevi

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Opisuje se sinteza L-β-metionina (I), t. t. 166—167°, $[\alpha]_D^{20}$ —23° (c, 1.535 u vodi) i L-β-homodjenkolne kiseline (II), t. t. 213°, $[\alpha]_D^{25}$ —110° (c, 0.71 u vodi), polazeći od *S*-benzil-L-β-homocisteina[11].

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