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TECHNICAL SYNTHESSES OF SULFUR CONTAINING AMINO ACIDS

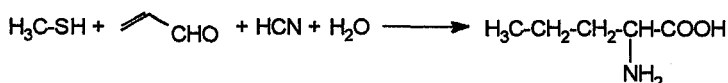
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Abstract About 25 % of the total production of amino acids world wide are sulfur containing amino acids. The applications, the technical syntheses and production methods are discussed with selected examples.

Amino acids are used as nutrition or feed additives, as basis of polymers, cosmetics, pharmaceuticals, and pesticides. The production of amino acids can be done by total chemical synthesis, by a microbiological or enzymatic route or by hydrolysis of natural proteins. About 25 % of the total production of amino acids worldwide are sulfur containing amino acids. In this respect the D,L-methionine and the racemic hydroxyanalogue of methionine (MHA) take by far the main share; in contrary cysteine and D-penicillamine are smaller representatives, which will be reviewed in this presentation.

D,L-methionine and D,L-MHA are used predominately as feed additives and are produced by total chemical syntheses. Starting materials are acrolein, methylmercaptane and hydrogen cyanide; the intermediate 5-(2-methylmercaptoethyl)-hydantoin is hydrolyzed to an alkali salt of D,L-methionine; acidification of the reaction mixture gives the free amino acid. The overall chemical equation is:



The technical production can be performed by a completely closed process recycling all auxiliary chemicals; a so-called process integrated environmental protection procedure.

In the body racemic D,L-methionine is enzymatically converted to L-methionine via the corresponding keto-acid.

The same is observed with the hydroxyanalogue of methionine (MHA); therefore this compound is also used as a „methionine“ feed additive. The technical synthesis is based on the hydrolysis of the cyanohydrin of methylmercaptopropionaldehyde. After separation of ammonium salts, which are formed as by-products, the material is purified, and adjusted to an 88 % aqueous product. A new route yields a liquid concentrate (about 100 % active material) which can be used as a convenient transportation form and readjusted to the commercial material or blended with other feed additives (eg. methionine, salts of MHA etc.).

D-Penicillamine is used as a basic therapeutic drug for treatment of rheumatic arthritis. Based on fundamental research of Prof. Asinger a technical total synthesis was elaborated by Degussa. The key intermediate 2-isopropyl-5,5-dimethylthiazolin-3 is produced in one step of isobutyric aldehyde, ammonia and elementary sulfur. Addition of hydrogen cyanide to the C=N-double bond gives a cyclic aminonitrile which is hydrolyzed to D,L-penicillamine. The resolution of the optical enantiomers is performed by formation of diastereomeric salt pairs with an optical active amine. The salt pairs are separated by selective crystallization, which yields pure D-penicillamine after work-up.

Based on that knowledge a new synthesis for (D)L-cysteine was elaborated in a similar way.

All mentioned amino acids can be basic materials for the preparation of further derivatives, like homocysteinethiolactone, D-penicillamine containing peptides, and S-carboxymethylcysteine, which are used as pharmaceuticals.