C-28

PREPARATIVE SEPARATION OF 4-FLUOROGLUTAMIC ACID STEREOISOMERS

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A method for separation of 4-fluoroglutamic acid stereoisomers, based on the fractional crystallization of their suitable derivatives, has been developed. The synthetically prepared 1:1 erythro/threo mixture was first converted to the dimethyl ester hydrochlorides, from which the erythro-diastereomer crystallized preferentially. Material of at least 99% diastereomeric purity was thus obtained after several recrystallizations. On mild acid hydrolysis, the racemic erythro-4-fluoroglutamic acid was prepared. From the mother liquors there was recovered free 4-fluoroglutamic acid, enriched in the threo-diastereomer to 77%. On treatment with brucine, the pure D-enantiomer of threo--4-fluoroglutamic acid was separated through its less soluble salt.

The erythro/threo ratio of the individual fractions was determined by GLC, using the fast and quantitative conversion into the well-separable trans-cis methyl 3-fluoro-2-pyrrolidone -5-carboxylates. Both diastereomers of 4-fluoroglutamic acid were analytically separated into enantiomers by HPLC on a chiral mobile phase, after conversion to the 5-methyl esters and subsequent dansylation.