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SYNTHESIS OF 4' -AMINO-4' -DEOXY ANALOG OF PANTOTHENIC ACID

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Summary: The synthesis of D- and L-N-(4-amino-3, 3-dimethyl-2-hydroxybutyryl)- β-alanine (7) is described. Compound 7 is an analog of pantothenic acid in which the 4' -hyroxy group is replaced by amino group. The synthetic sequence leading to 7 involved the synthesis DL-4-amino-3,3-dimethyl-2-hydroxybutyric acid and its resolution. Coupling of N-benzyloxycarbonyl N-hydroxysuccinimide ester (5) with β-alanine and followed by removal of the protecting group gave 7.

D-Pantothenic acid is an important constituent of Coenzyme A (CoA) and acyl carrier protein. Phosphorylation of pantothenic acid with the formation of D-pantothenate 4' -phosphate is the first step in CoA biosynthesis from D-pantothenic acid [1], catalysed by pantothenate kinase [2]. We believe that it would be highly desirable to have an analog of D-pantothenic acid containing an amino group at the 4' position instead of hydroxy group in order to investigate structural specificity of D-pantothenate kinase. However, no examples of 4' -amino-4' -deoxy analogs of pantothenic acid have been reported.

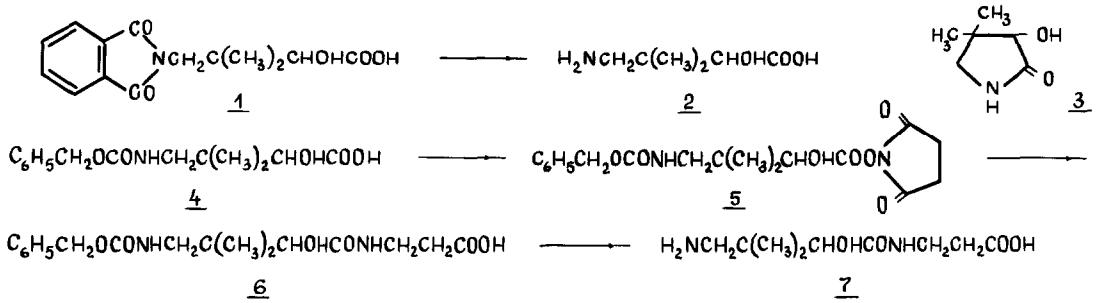
In a continuing program to explore the effect structural modification on the activity of pantothenic acid [3], we synthesized N-(4-amino-3,3-dimethyl-2-hydroxybutyryl)- β-alanine (7). In view of it became necessary for us to search for the convenient method of preparation of 4-amino-3,3-dimethyl-2-hydroxybutyric acid (2) and its N-protected derivatives.

It is well known [4] that the reaction of γ-butyrolactone with potassium phthalimide affords 4-phthalimidobutyric acid in fairly good yield. The fact the cleavage of CH_2O bond of the γ-butyrolactone and simultaneous formation of the CH_2N bond had occured in the course of this reaction prompted us to investigate the alkylation of potassium phthalimide with D-pantolactone.

Fusion of D-pantolactone with potassium phthalimide at 140-150° or performing this reaction in DMF at 150° afforded racemic 4-phtaloylamino-3,3-dimethyl-2-hydroxybutyric acid (1) in 77% yield, mp 163-165°. Resolution of 1 was accomplished by conversion into its L-(+)-threo-1-(p-nitrophenyl)-2-amino-1,3-propandiol salt followed by recrystallisation from ethanol. Hydrolysis of

optically pure salts with 10% HCL gave stereoisomers of 1 with $[\alpha]_{589}^{23}$ + 10,9° and -9,27° (c 1,2, ethanol). Removal of the phthaloyl group in isomers by heating with hydrazine hydrate in ethanol for 5 hrs led to the desired products 2 with $[\alpha]_{589}^{23}$ -14,5° and +14,0° (c 1, H_2O).

The structure of 2 thus obtained was confirmed by its IR and NMR spectrum and elemental analysis [5]. The specific rotation of γ-lactam (3) ($[\alpha]_{589}^{23}$ + 30°) prepared from (+)-2 was in good agreement with the value (+25,6°) reported for this substance prepared from D-pantolactone [6]. Taking into account the above mentioned result (+)-2 is undoubtedly assigned D-configuration.



Since attempts to use 1 as an intermidate in the synthesis of analog 7 failed, N-benzyloxycarbonyl derivative 4 was synthesized by conventional procedure from (+)-2. Treatment of 4 with N-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide in dichlormethane gave N-hydroxysuccinimide ester (5). Condensation was performed by treating 5 with β-alanine in ethanol-H_2O fof 18 hrs at room temperature. The reaction mixture was concentrated and solution was acidified to pH 2 by the addition of 5 N HCL and the precipitate formed was filtered. One crystallisation from AcOEt afforded a crystalline substance which proved to be N-benzyloxycarbonyl derivative (6) (63%), mp 145-146°, $[\alpha]_{589}^{23}$ + 20,3° (c 0,5,ethanol). The final conversion of 6 to D(+)-1 was effected by catalytic hydrogenation (5% Pd/C), mp 174-176°, $[\alpha]_{589}^{23}$ +22° (c 5,45, H_2O). Treatments similar to those previosly described successfully provided L(-)-1, $[\alpha]_{589}^{23}$ -25,3° (c 5,45, H_2O) from L(-) 2.

Synthesis and biological evalution of novel derivatives of aminopantothenic acid will be reported from this laboratory.

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