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N-SUBSTITUTED PYRROLIDONE-CARBOXYLATES IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE GABA DERIVATIVES AND α-PYRROLIDONE

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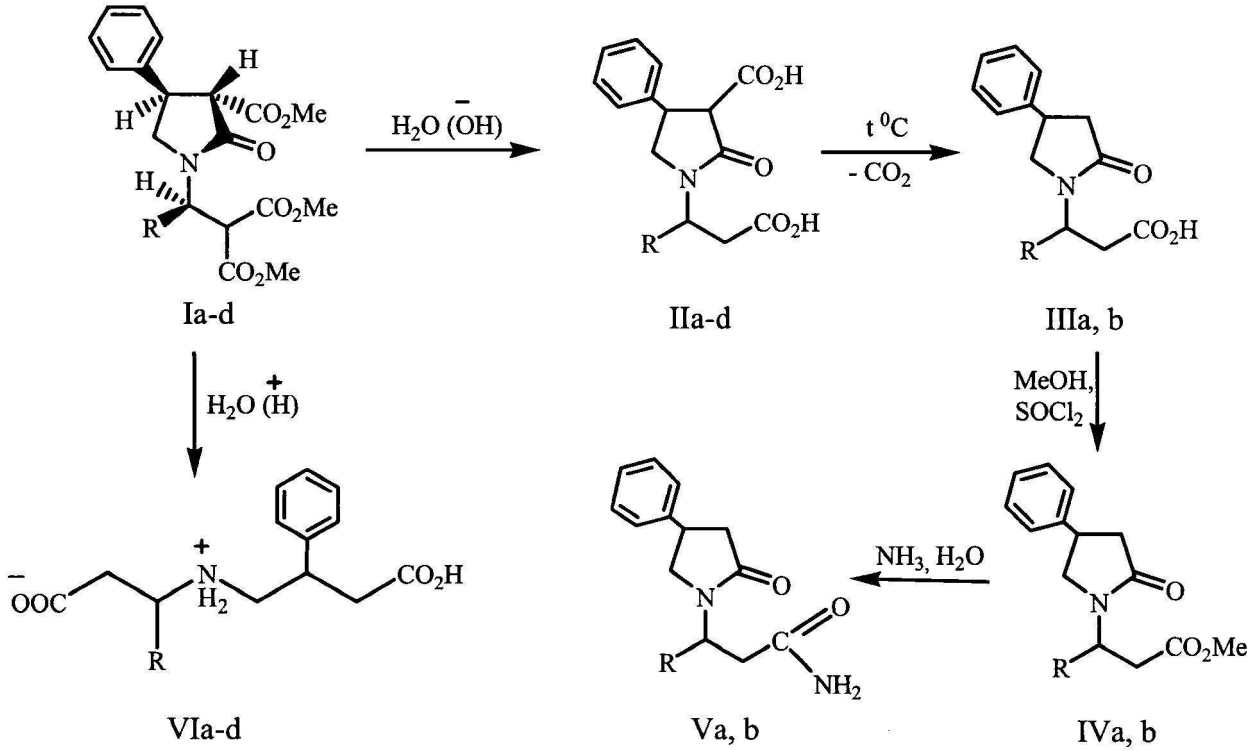
Lots of chemists and pharmacologists study structural analogs of GABA and α-pyrrolidone. The great interest towards these compounds is due to their pharmacological properties, such as psychotropic, nootropic, cardiovascular and other activities. [1-4]. For example, γ-amino-butyric acid (Gammalone) is used to treat neuropathy; its β-phenyl derivative (Phenibut) is a good nootropic and cardiovascular medicine [1-4]. The pyrrolidone cycle is a part of nootropic drug Piracetam [1-4] and of its phenyl derivative Carphedon (Phenotropil) [5]. Poly N-vinyl-pyrrolidone can be used as a plasma substitute, a drug carrier; it is also used to excrete toxins from the body [1-4].

Pyrrolidone-carboxylates are accessible precursors for the synthesis of new derivatives of α-pyrrolidone and γ-amino-butyric acid. N-dialcoxy-carbonyl-ethyl substituted 3-pyrrolidone-carboxylates (a-d) are quite interesting in this aspect since these compounds are precursors of a new type of GABA and Piracetam analogs. We have synthesized these substances as two individual diastereomers by the reaction of 3-methoxy-carbonyl-4-phenyl-2-pyrrolidone with 2-aryl(heteryl)-1,1-dimethoxy-carbonyl-ethens [6].

In the present work we have studied the behavior of diastereo-homogeneous N-dimethoxy-carbonyl-ethyl-pyrrolidone-carboxylates (1a-d) under the conditions of basic and acidic hydrolysis. Thus, refluxion of compounds (1a-d) in 10% alcohol water solution of sodium hydroxide proceeds with saponification followed by decarboxylation of one of the carboxyl-groups of carboxy-ethyl fragment. This has resulted in the synthesis (83–97%) of pyrrolidone-carbonic acids (IIa-d). These are colorless or light yellow water soluble crystals.



R = C_6H_5 (a), 4-ClC_6H_4 (b), 4-$NO_2C_6H_4$ (c), 3-pyridyl (d).

Compounds (IIa, b) being heated under reduced pressure up to the temperatures higher than their melting points undergo decarboxylation of the carboxyl group at C^3 atom of the heterocycle which results in the formation of pyrrolidone-carbonic acids (IIIa, b) with yields up to 71%. The latter have been used for the synthesis of Piracetam analogs. Thus, (IIIa, b) were esterified by methanol in the presence of thionyl chloride; esters (IVa, b) formed (up to 70% yeilds) were aminated by ammonium aqueous solution which resulted in the synthesis of 1-[1'-aryl(heteryl)-2'-carbamoyl-ethyl]-4-phenyl-2-pyrrolidones (Va, b) (up to 86% yileds).

Unlike basic hydrolysis the refluxion of N-substituted pyrrolidone-carboxylates (Ia-d) in 6N hydrochloric acid led to saponification, decarboxylation and pyrrolidone cycle opening. As a result new 4-[1'-aryl(heteryl)-2'-carboxy-ethyl-amino]-3-phenyl-butanoic acids (VIa-d) were formed with up to 83% yields. HABA derivatives (VIa-d) are colorless crystals with high melting points.

The structure of all compounds synthesized is proved by IR and NMR ^1H spectroscopy methods.

The structural similarity of the compounds formed with Carphedon and Phenibut, which are widely used in medicine, makes these materials potentially biologically active, they can be recommended for the following extended pharmacological studies.

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