Abstract

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The Faculty of Mathematics and Natural Sciences
Pharmaceutical Institute, Pharmaceutical Chemistry I
Diploma Thesis

Synthesis of Functional Derivatives of Malonic Acid as Buildings Blocs for Elastase Inhibitors

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Human leukocyte elastase (HLE) is a serine protease, which plays an important role in inflammatory diseases. Low molecular weight inhibitors can be therapeutically used for example for the treatment of chronic obstructive pulmonary diseases. In this thesis, azetidin-2,4-dione derivatives should be prepared as HLE inhibitors. In particular, 3-(benzyloxycarbonylamino)-3-ethyl-*N*-phenyl-azetidine-2,4-dione should be synthesized. The protected amino group was expected to increase the peptidic character of this molecule and thus, affinity to HLE.

The starting compound was 2-aminomalonic acid diethylester hydrochlorid. The amino function was protected in the first step, followed by alkylation and then hydrolysis of 2-(benzyloxycarbonylamino)-2-ethylmalonic acid diethylester to 2-(benzyloxycarbonylamino)-2-ethylmalonic acid. Both the ester of 2-(benzyloxycarbonylamino)malonic acid and the 2-(benzyloxycarbonyl-amino)ethylmalonic acid showed in their ^{1}H NMR spectra a multiplet in place of the expected quartet. This phenomenon was explained as a result of the prochiral center present in both molecules. The 2-(benzyloxycarbonylamino)-2-ethylmalonic decarboxylated at 60 °C to 2-(benzyloxycarbonylamino)butyric acid.

The 2-(benzyloxycarbonylamino)-2-ethylmalonic acid was reacted with oxalyl chloride to give the acid chloride and then *in situ* with aniline to a carbamoylhydantoine, namely 4-ethyl-2,5-dioxo-*N*,1-diphenylimidazolidine-4-carboxamide. The postulated cyclic intermediate, a 2-benzyloxy-5(4*H*)-oxazolone derivative, has probably been attacked by aniline at the benzyl group to afford *N*-benzylaniline. The reaction conditions were optimal when 3 equivalents of aniline were used at room temperature. Similar carbamoylhydantoins should be synthesized in

future experiments. Several further experiments were performed, but they were not successful.