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On the *Michael* Type Addition of Dipeptides to 4-Oxo-4-phenyl-2-butenoic Acid Derivatives

Short Communication

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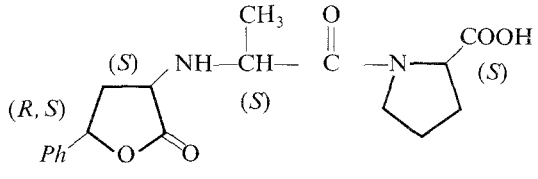
The title reaction afforded the adducts **3** in variable selectivity, but the isomers of (*S,S,S*)-configuration were easily isolated; the reversibility of the reaction permits the recovery of the starting materials from the mother liquor. High selectivity has been observed in one case only.

[Keywords: Michael type addition; 4-Oxo-4-phenyl-2-butenoic acids; (S)-Alanyl-(S)-proline; (S)-Lysyl-(S)-proline]

Zur Michael-ähnlichen Addition von Dipeptiden an Derivate der 4-Oxo-4-phenyl-2-butensäure (Kurze Mitteilung)

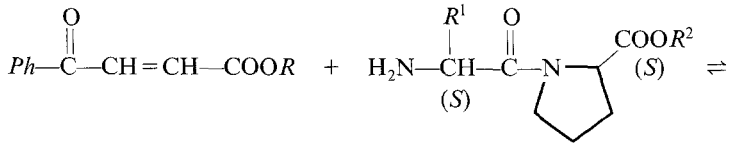
Die Titelreaktion liefert die Addukte **3** in unterschiedlicher Selektivität; die Isomeren mit (*S,S,S*)-Konfiguration konnten jedoch einfach isoliert werden, und die Reversibilität der Reaktion ermöglicht die Rückgewinnung der Ausgangsstoffe. Eine hohe Selektivität wurde nur in einem Fall beobachtet.

The title reaction was used by *Preston* and *Carling* [1] for the preparation of angiotensin-converting-enzyme (*ACE*) inhibitors, and the adducts have been separated by chromatographic methods. *Greenlee* has studied this reaction; a mixture (1:1) of diastereomers was obtained (**3**, R and R^2: H, R^1: CH_3) which were separated on an ion exchange resin [2].

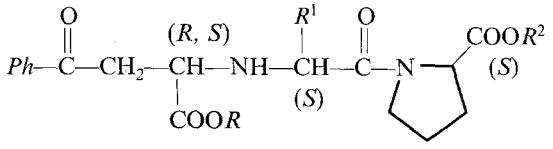


RGH-0399 (separated as maleate salts)

In order to synthesize our new *ACE*-inhibitors (RGH-0399) [3] it was necessary to study the title reaction; we have found that the adducts **3** of (*S,S,S*)-configuration could be separated easily via their salts, and the *Michael* type addition of dipeptides to 4-oxo-4-phenyl-2-butenoic acid was found to be reversible.



1 **2**



3

(*Ph*: phenyl, *R*: H, ethyl, sec-butyl, (—)menthyl,
R^1: CH_3, $(CH_2)_4NHCOO(CH_3)_3$, R^2: *tert*-butyl, benzyl)

We have investigated the *Michael* type addition of (*S*)-alanyl-(*S*)-proline derivatives to componds **1**. The adducts of (*S,S,S*)-configuration could be easily separated as maleate salts, and in one case, *R*: (—)menthyl, adduct **3** was separated as a base [**3**, *R*: (—)menthyl, R^1: CH_3, R^2: *tert*-butyl; m.p.: 133–134 °C, $[\alpha]_D^{25}$: $-112°$ ($c = 1$, methanol)]. The diastereoselectivity was generally between 20–50% (de) and was not essentially influenced by the size of the group *R*, and by the (*E*) and (*Z*)-configuration of compounds **1**, or by the protecting group R^2 in compounds **2**. Because of the reversibility of the reaction, the diastereomer of (*R, S, S*)-configuration could be easily decomposed by heating (at 80 °C) of the mother liquor, i.e. the peptide-component of the (*R, S, S*)-diastereomer could be recovered nearly in quantitative yields. A typical procedure is the following:

1.50 g (5 mmol) of (*S*)-alanyl-(*S*)-prolinebenzylester hydrochloride in 20 ml benzene was reacted with 1.04 g (5 mmol) of (*E*)-ethyl-4-oxo-4-phenyl-2-butenoate, and at +5 °C 0.7 g (5 mmoles) of triethylamine was added to the reaction mixture. After 5 h at RT the solvent was evaporated and the residue was taken up in 10 ml of ethyl acetate, after adding 0.58 g of maleic acid N-[1(*S*)-ethoxycarbonyl-3-phenyl-3-oxo-propyl]-(*S*)-alanyl-(*S*)-prolinebenzylester maleate was isolated: 2.1 g (71%), m.p. 136–138 °C, $[\alpha]_D^{25}$: $-49.3°$ ($c = 1$,

methanol). The mother liquor was refluxed for 3 h, then cooled to +5 °C and 0.46 g (82%) of (*S*)-alanyl-(*S*)-prolinebenzylester maleate was isolated, m.p. 146–149 °C, $[\alpha]_D^{25}$: −77.3° (*c* = 1, methanol).

Nearly the same conditions were found in the *Michael* type additions od (*S*)-lysyl-(*S*)-proline derivatives if the compounds **1** were used as esters. The only selective addition was observed when the free acidic form of **1** was used; in this case, however, the adduct of (*R,S,S*)-configuration was obtained in a yield of 90% [**3**, *R*: H, R^1: $(CH_2)_4NHCOO(CH_3)_3$, R^2: *tert*-butyl; m.p. 125–126 °C (decomp.), $[\alpha]_D^{25}$: −36.7° (*c* = 1, CH_2Cl_2)]. In order to prove the configuration on the latter compound, it was hydrogenated on Pd/C to afford the epimer of lisinopril [4]: m.p. 146–148 °C, $[\alpha]_D^{25}$: −43.1° (*c* = 1, methanol). The ^{13}C n.m.r. chemical shifts were found to be identical to those described in the literature [4].

Acknowledgement

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References

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