Reaction of $N$-Acyl-$\gamma$-aminobutyric Acids with 3-Ethoxycarbonylbenzotriazole 1-Oxide

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Abstract—Reactions of $\alpha,\beta$-dehydrodipeptides containing a terminal $\gamma$-aminobutyric acid residue with 3-ethoxycarbonylbenzotriazole 1-oxide at 90–100°C result mainly in cleavage of the peptide bond. In the cold, the corresponding ethyl ester and $N$-acyl-$\gamma$-butyrolactam are formed. Analogous reactions with $N$-benzoyl- and $N$-benzyloxycarbonyl-$\gamma$-aminobutyric acids leads to formation of the corresponding ethyl esters.

In the present study we examined the possibility for synthesizing $N$-acylbutyrolactams with the use of 3-ethoxycarbonylbenzotriazole 1-oxide (I). For this purpose, $N$-substituted $\gamma$-aminobutyric acids IIa–IId were treated with compound I in acetonitrile in the presence of triethylamine (Scheme 1).

Both at room temperature (24 h) and on heating the reaction mixture under reflux (water bath, 3 h), from $N$-benzoyl- and $N$-benzyloxycarbonyl-$\gamma$-aminobutyric acids IIa and IIb we obtained the corresponding ethyl esters IIIa and IIIb. The yields of esters IIIa and IIIb were fairly high, 71 and 80%, respectively. According to the TLC data, the reactions of $N$-benzoyl-$\alpha,\beta$-dehydro-$O$-alkyltyrosyl-$\gamma$-aminobutyric acids IIc and IId with benzotriazole oxide I gave mixtures of products. When the reactions were performed under reflux, the major products were 4-(4-alkoxyphenyl)methylene-2-phenyl-4,5-dihydro-1,3-oxazol-5-ones (V). Their structure corresponds to the dehydroaminoacid residues of initial dipeptides IIc and IId. In other words, cleavage of the peptide bond is observed. The yield of products Vc and Vd depends on the reaction time, temperature, and amount of triethylamine in the mixture (Table 1).

We failed to examine the reaction with I of $N$-benzoyl-$\alpha,\beta$-dehydro-$O$-methyltyrosyl-$\gamma$-aminobutyric acid IId, for it is poorly soluble in acetonitrile. In the reaction with $N$-benzoyl-$\alpha,\beta$-dehydro-$O$-isopropyltyrosyl-$\gamma$-aminobutyric acid (IIc) at room temperature (24 h), the yield of oxazolone Vc did not exceed 13%. Apart from compound Vc, a mixture of ester IIIc ($R_f$ 0.28) and $\gamma$-butyrolactam IVc ($R_f$ 0.41) at a ratio of 7 : 3 (according to the $^1$H NMR data) was isolated (see figure and Table 2).

In order to refine the product composition, ester IIIc and lactam IVc were also synthesized by independent methods. The reaction of acid IIc with ethyl acetate in the presence of sulfuric acid gave 60% of ester IIIc. TLC analysis of the reaction mixture showed that 4-(4-isopropoxybenzylidene)-2-phenyl-4,5-dihydro-1,3-oxazol-5-one (Vc) ($R_f$ 0.89) was also formed in trace amounts.

Scheme 1.

![Scheme 1](image-url)
Table 1. Yields of 4,5-dihydro-1,3-oxazol-5-ones Vc and Vd in the reactions of N-substituted α,β-dehydrodi-peptides IIc and IId with 3-ethoxycarboylnbenzotriazole 1-oxide

<table>
<thead>
<tr>
<th>Comp. no.</th>
<th>Reaction time, h</th>
<th>Molar ratio I:Et₃N</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80°C</td>
<td>25°C</td>
<td></td>
</tr>
<tr>
<td>IId</td>
<td>3</td>
<td>–</td>
<td>1:2</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>–</td>
<td>1:2</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>–</td>
<td>1:4</td>
</tr>
</tbody>
</table>

γ-Butyrolactam IVc was obtained in 71% yield by treatment of acid IIc with acetic anhydride in acetonitrile in the presence of triethylamine at 18–20°C (reaction time 24 h). According to the TLC data, oxazole Vc was also formed. The structure of butyrolactam IVc was proved by the ¹H and ¹³C NMR spectra. The ¹H signals were assigned on the basis of the two-dimensional COSY spectra, and the ¹³C signals, using two-dimensional ¹³C–¹H heteronuclear correlation technique (2D-HETCOR). The arrangement of the substituents at the double bond was determined from the 2D-NOESY spectra which showed that the NH hydrogen atom appears in the vicinity of the ortho-protons of two benzene rings (9-H and 7-H); the corresponding cross peaks were observed. The vinyl proton (8-H) located trans with respect to the NH group gives no cross peak with the latter. These data indicate Z configuration of compound IVc.

Thus the reaction of α,β-dehydrodipeptide IIc with benzotriazole oxide I at room temperature results mainly in esterification and cyclization of the initial acid, whereas under reflux cleavage of the peptide bond occurs.

In order to elucidate the mechanism of peptide bond cleavage in α,β-dehydrodipeptides IIc and IId, acetonitrile solutions of IIIc and IVc containing an equimolar amount of triethylamine were refluxed on a water bath. TLC analysis of the reaction mixture obtained from ester IIIc showed no changes over a period of 5 h. In the reaction with lactam IVc, spots with Rₛ 0.19 and 0.89 appeared on the chromatogram in 5 min. The first of these corresponds to pyrrolidone, and the second, to oxazole Vc which (after 5 h) was isolated in 64% yield. We can conclude that the reaction of I with α,β-dehydrodipeptides IIc and IId involves formation of mixed anhydride VI which either loses carbon dioxide to give ester III or undergoes cyclization into lactam IV. Elimination of the pyrrolidone fragment from IV on heating yields oxazole V (Scheme 2).

In the mass spectrum of lactam IVc we observed no molecular ion peak but those from fragment ions corresponding to oxazole Vc and pyrrolidone.

**EXPERIMENTAL**

The IR spectra were recorded on a Specord 75IR spectrometer in mineral oil. The ¹H and ¹³C NMR spectra were obtained on a Mercury 300 instrument (which was supplied by the CRDF foundation in the framework of the RESC 17-5 program). The purity of the products was checked by TLC on Silufol UV-254 plate using 1:1 diethyl ether–benzene as eluent; spots were visualized with UV light and iodine vapor. 3-Ethoxycarbonylbenzotriazole 1-oxide (I) was prepared by the procedure reported in [1]; N-substituted α,β-dehydrodipeptides IIa–IId were synthesized as described in [2].