Russian Journal of Organic Chemistry, Vol. 37, No. 3, 2001, pp. 351–355. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 3, 2001, pp. 379–382.

Reaction of *N*-Acyl-γ-aminobutyric Acids with 3-Ethoxycarbonylbenzotriazole 1-Oxide

V. O. Topuzyan[1], G. Yu. Khachvankyan[1], A. S. Kotolikyan[1], and G. A. Panosyan[2]

[1] *Institute of Fine Organic Chemistry, Armenian National Academy of Sciences, pr. Azatutyan 26, Erevan, 375014 Armenia*

[2] *Molecular Structure Research Center, Armenian National Academy of Sciences*

Received April 7, 1999

Abstract—Reactions of α,β-dehydrodipeptides containing a terminal γ-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-γ-butyrolactam are formed. Analogous reactions with *N*-benzoyl- and *N*-benzyloxycarbonyl-γ-aminobutyric acids leads to formation of the corresponding ethyl esters.

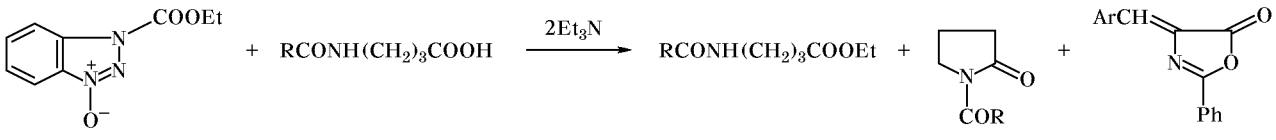
In the present study we examined the possibility for synthesizing *N*-acylbutyrolactams with the use of 3-ethoxycarbonylbenzotriazole 1-oxide (**I**). For this purpose, N-substituted γ-aminobutyric acids **IIa**–**IId** were treated with compound **I** in acetonitrile in the presence of triethylamine (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-γ-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-α,β-dehydro-*O*-alkyltyrosyl-γ-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 dehydroamino-acid 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-α,β-dehydro-*O*-methyltyrosyl-γ-aminobutyric acid **IId**, for it is poorly soluble in acetonitrile. In the reaction with *N*-benzoyl-α,β-dehydro-*O*-isopropyltyrosyl-γ-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 γ-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.



I **IIa–IId** **IIIa–IIIc** **IVc** **Vc, Vd**

R = Ph (**a**), $PhCH_2O$ (**b**), PhCONHC=CHC_6H_4OPr-*i*-4 (**c**), PhCONHC=CHC_6H_4OMe-4 (**d**).

1070-4280/01/3703-0351 $25.00 © 2001 MAIK "Nauka / Interperiodica"

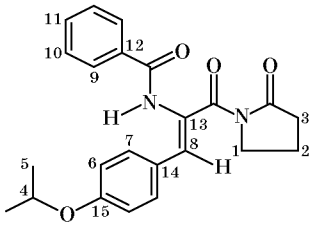
Table 1. Yields of 4,5-dihydro-1,3-oxazol-5-ones **Vc** and **Vd** in the reactions of *N*-substituted α,β-dehydrodipeptides **IIc** and **IId** with 3-ethoxycarbonylbenzotriazole 1-oxide

Comp. no.	Reaction time, h		Molar ratio **I**:Et_3N	Yield, %
	80°C	25°C		
IIc	5	–	1:2	67
	–	24	1:2	13
IId	3	–	1:2	70
	5	–	1:2	72
	5	–	1:4	45

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 ^{13}C NMR spectra. The ^1H signals were assigned on the basis of the two-dimensional COSY spectra, and the ^{13}C signals, using two-dimensional ^{13}C–^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**.

Table 2. ^1H NMR spectra of ethyl ester **IIIc** and *N*-acyllactam **IVc**

Group	Chemical shifts δ, ppm (*J*, Hz)	
	IIIc	**IVc**
α-CH_2 (γ-Abu)	2.32 t (7.5)	3.43 t
β-CH_2 (γ-Abu)	1.75 q (7.1)	1.92 q (7.6)
γ-CH_2 (γ-Abu)	3.20 q (6.6)	3.73 t (7.2)
NH (γ-Abu)	7.86 t (6.0)	–
NH (Δ-Tyr)	9.62 s	10.03 s
β-CH (Δ-Tyr)	7.20 s	6.68 s
CHO	4.63 m (6.6)	4.63 m
$C(CH_3)_2$	1.25 d (6.6)	1.25 d
OCH_2	4.06 q (7.2)	–
CH_3 (OEt)	1.17 (7.2)	–



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.

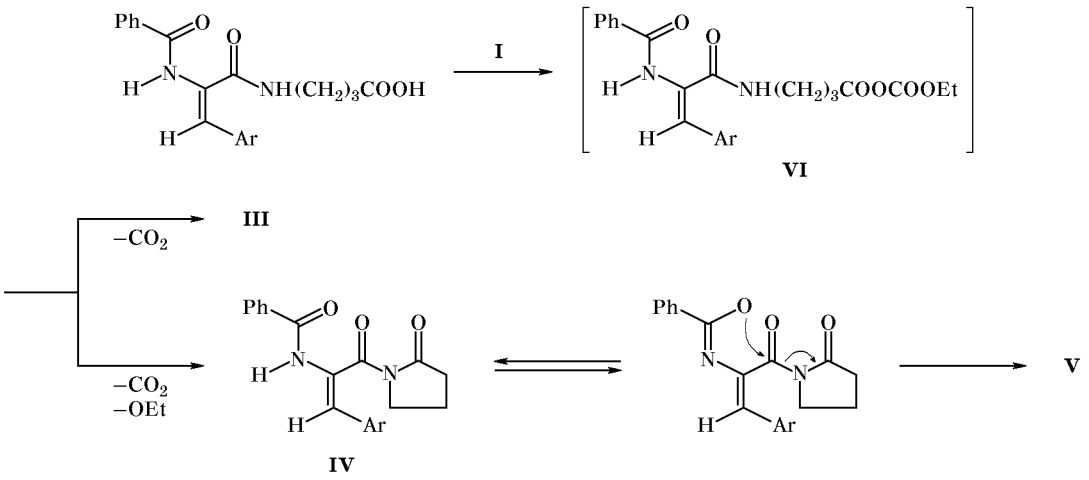
In order to elucidate the mechanism of peptide bond cleavage in α,β-dehydrodipeptides **IIc** and **IId**, acetonitrile solutions of **IIIc** and **IVc** containing an equimolar amount of triethylamine were refluxed on a water bath. TLC analysis of the reaction mixture obtained from ester **IIIc** showed no changes over a period of 5 h. In the reaction with lactam **IVc**, spots with R_f 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

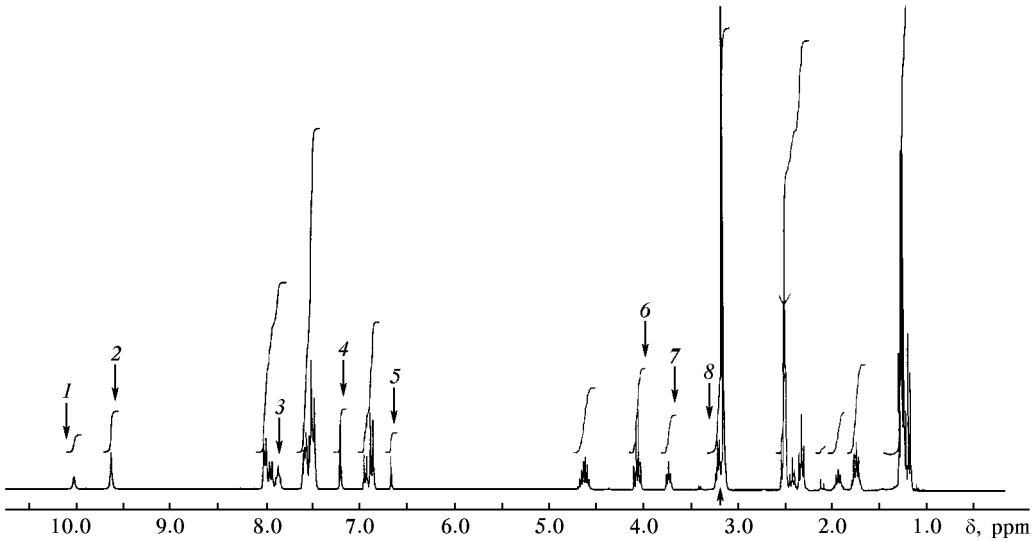
The IR spectra were recorded on a Specord 75IR spectrometer in mineral oil. The ^1H and ^{13}C NMR spectra were obtained on a Mercury 300 instrument (which was supplied by the CRDF foundation in the framework of the RESC 17-5 program). The purity of the products was checked by TLC on Silufol UV-254 plate 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].

Scheme 2.



Ethyl *N*-benzoyl-γ-aminobutyrate (IIIa). To a solution of 1 g (4.8 mmol) of acid **IIa** and 0.97 g (9.6 mmol) of triethylamine in 15 ml of acetonitrile we added 0.99 g (4.8 mmol) of reagent **I**, and the mixture was refluxed for 3 h on a water bath. The solvent was removed, the residue was dissolved in 80 ml of chloroform, and the solution was treated with a 5% solution of sodium hydrogen carbonate (2 × 25 ml), water (25 ml), 1 N hydrochloric acid (2 × 25 ml), and water again (until neutral reaction). The organic phase was dried over calcium chloride and evaporated under reduced pressure. The residue was an oily substance. Yield 0.8 g (71%). IR spectrum, ν, cm^{-1}: 3265 (N−H), 1750 (C=O, ester), 1640 (C=O, amide). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.82 t (3H, CH_3, *J* = 7.2 Hz), 1.58 q (2H, β-CH_2, γ-Abu, *J* = 7.1 Hz), 2.00 t (2H, α-CH_2, γ-Abu, *J* = 7.5 Hz), 3.06 q.d (2H, γ-CH_2, γ-Abu, *J* = 6.4 Hz), 3.68 q.d (2H, OCH_2, *J* = 7.2 Hz), 6.40 t (1H, NH, *J* = 6.0 Hz), 6.87–7.73 m (5H, H_{arom}). Found, %: N 6.09. $C_{13}H_{17}NO_3$. Calculated, %: N 5.95. When the reaction was performed at room temperature, the yield of **IIIc** was 67%.

Ethyl *N*-benzyloxycarbonyl-γ-aminobutyrate (IIIb) was synthesized in a similar way by heating under reflux 1 g (4.21 mmol) of *N*-benzyloxycarbonyl-



^{1}H NMR spectrum of a mixture of ethyl *N*-benzoyl-α,β-dehydro-*O*-isopropyltyrosyl-γ-aminobutyrate (**IIIc**) and *N*-(*N'*-benzoyl-*O*-isopropyl-α,β-dehydrotyrosyl)-γ-butyrolactam (**IVc**): (*1*) NH (Δ-Tyr, **IVc**), (*2*) NH (Δ-Tyr, **IIIc**), (*3*) NH (γ-Abu, **IIIc**), (*4*) CH=C (Δ-Tyr, **IIIc**), (*5*) CH=C (Δ-Tyr, **IVc**), (*6*) OCH_2 (**IIIc**), (*7*) NCH_2 (**IVc**), (*8*) NCH_2 (**IIIc**).

γ-aminobutyric acid (**IIb**), 0.85 g (8.42 mmol) of triethylamine, and 0.87 g (4.21 mmol) of reagent **I**. Yield 81%. IR spectrum, ν, cm^{-1}: 3255 (N–H), 1750 (C=O, ester), 1685 (C=O, amide). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 t (3H, CH_3, J = 7.2 Hz), 1.71 q (2H, β-CH_2, γ-Abu, J = 7.1 Hz), 2.20 t (2H, α-CH_2, γ-Abu, J = 7.5 Hz), 3.06 t (2H, γ-CH_2, γ-Abu, J = 6.5 Hz), 4.03 q (2H, OCH_2, J = 7.1 Hz), 5.00 s (2H, $ArCH_2O$), 5.86 br.s (1H, NH), 7.25 m (5H, H_{arom}). Found, %: N 5.04. $C_{14}H_{19}NO_4$. Calculated, %: N 5.28.

***N*-Benzoyl-*O*-isopropyl-α,β-dehydrotyrosine ethyl ester (IIIc).** A mixture of 1 g (2.4 mmol) of *N*-benzoyl-*O*-isopropyl-α,β-dehydrotyrosine (**IIc**) and 0.2 ml of sulfuric acid in 7 ml of ethyl acetate was stirred for 24 h at room temperature. The light yellow solution was diluted with ethyl acetate (50 ml), treated with a 5% solution of sodium hydrogen carbonate (2 × 25 ml) and with water until neutral reaction, and dried over sodium sulfate. The solvent was removed under reduced pressure, the residue was ground with ether (2 × 10 ml), and the precipitate was filtered off and washed with ether. Yield 0.6 g (56%). mp 107–108°C. R_f 0.45. IR spectrum, ν, cm^{-1}: 3235 (N–H), 1750 (C=O, ester), 1650 (C=O, amide), 1615 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 t (3H, CH_3, J = 7.2 Hz), 1.25 d (6H, CMe_2, J = 6.6 Hz), 1.75 q (2H, β-CH_2, γ-Abu, J = 7.1 Hz), 2.32 t (2H, α-CH_2, γ-Abu, J = 7.4 Hz), 3.20 q (2H, γ-CH_2, γ-Abu, J = 6.5 Hz), 4.06 q (2H, OCH_2, J = 7.2 Hz), 4.63 m (1H, OCH), 7.20 s (1H, β-CH, Δ-Tyr), 6.85–8.20 m (9H, H_{arom}), 7.86 t (1H, NH, γ-Abu, J = 6.0 Hz), 9.62 s (1H, NH, Δ-Tyr). From the ether solution we isolated 0.09 g (12%) of oxazolone **Vc**. mp 151–153°C. R_f 0.89.

Reaction of *N*-substituted α,β-dehydrodipeptides IIc and IId with 3-ethoxycarbonylbenzotriazole 1-oxide (I). *a*. A mixture of 2.5 mmol of *N*-benzoyl-α,β-dehydrodipeptide **IIc** or **IId**, 5–10 mmol of triethylamine, 2.5 mmol of compound **I**, and 10 ml of acetonitrile was refluxed for 3–5 h on a water bath. The solvent was removed, the residue was dissolved in 50 ml of chloroform, and the solution was washed with a 5% solution of sodium hydrogen carbonate (2 × 25 ml), water (25 ml), 1 N hydrochloric acid (2 × 25 ml), and water again (until neutral reaction). The organic phase was dried with calcium chloride and evaporated, and the residue was recrystallized from ethanol.

4-*p*-Isopropoxybenzylidene-2-phenyl-4,5-dihydro-1,3-oxazol-5-one (Vc). mp 151–153°C [2]. IR spectrum, ν, cm^{-1}: 1778 (C=O), 1765 (C=N), 1642 (C=C). Found, %: C 74.53; H 5.89; N 4.21. $C_{19}H_{17}NO_3$. Calculated, %: C 74.25; H 5.57; N 4.56.

4-*p*-Methoxybenzylidene-2-phenyl-4,5-dihydro-1,3-oxazol-5-one (Vd). mp 157–159; published data [3]: mp 159–161°C. IR spectrum, ν, cm^{-1}: 1780 (C=O), 1767 (C=N), 1647 (C=C).

b. To a solution of 1 g (2.4 mmol) of *N*-benzoyl-*O*-isopropyl-α,β-dehydrotyrosine (**IIc**) and 0.49 g (4.8 mmol) of triethylamine in 15 ml of acetonitrile we added 0.5 g (2.4 mmol) of 3-ethoxycarbonylbenzotriazole 1-oxide (**I**), and the mixture was left to stand for 24 h at 18–20°C. It was then treated as described above in *a*. The residue was ground with ether (3 × 10 ml), and the precipitate was filtered off and washed with ether. The product was a colorless amorphous substance which was a mixture of two compounds (according to the TLC data) with R_f 0.24 and 0.44. The ^1H NMR spectrum of this mixture is shown in Fig. 1. After removal of the solvent, we isolated 0.1 g of yellow oxazolone **Vc**. mp 150–153°C. IR spectrum, ν, cm^{-1}: 1778 (C=O), 1765 (C=N), 1642 (C=C).

***N*-(*N*-Benzoyl-*O*-isopropyl-α,β-dehydrotyrosyl)-γ-butyrolactam (IVc).** Acetic anhydride, 0.49 g (4.8 mmol), was added to a solution of 1 g (2.4 mmol) of dipeptide **IIc** and 0.49 g (4.8 mmol) of triethylamine in 10 ml of acetonitrile, and the mixture was left to stand for 24 h at 18–20°C. The mixture was then treated as described above in *a*. The residue was ground with ether (2 × 10 ml), and the precipitate was filtered off and washed with ether. Yield 0.57 g (78%). mp 147–148°C (from acetonitrile). R_f 0.27. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.26 d (6H, CH_3, J = 6.0 Hz), 1.91 m (2H, β-CH_2, Abu), 2.42 t (2H, α-CH_2, Abu, J = 7.7 Hz), 3.70 t (2H, γ-CH_2, Abu, J = 7.2 Hz), 4.66 m (1H, CHO, J = 6.0 Hz), 6.67 s (1H, β-CH, Δ-Tyr), 6.94 d (2H, *m*-H, Δ-Tyr, J = 9.0 Hz), 7.59 d (2H, *o*-H, Δ-Tyr, J = 9.0 Hz), 7.94 d (2H, *o*-H, Bz, J = 8.2 Hz), 7.50 m (2H, *m*-H, Bz, J = 8.0 Hz), 7.59 m (1H, *p*-H, Bz, J = 8.0 Hz), 10.10 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6, 75.46 MHz), δ_C, ppm: 45.03 (C^3); 17.14 (C^2); 31.81 (C^3); 60.40 (C^4); 21.09 (C^5); 114.50 (C^6); 130.85 (C^7); 127.15 (C^8); 127.91 (C^9); 127.32 (C^{10}); 131.05 (C^{11}); 157.28 (C^{13}); 125.39, 128.07, 132.54 (C^{12}, C^{13}, C^{14}, C^{15}); 164.95, 167.12, 172.35 (CO).

Removal of the solvent from the ether solution gave 0.1 g (14%) of oxazolone **Vc** with mp 152–154°C. R_f 0.89.

Reaction of *N*-acyl-γ-butyrolactam IVc with triethylamine. A mixture of 0.5 h of compound **IVc** and 0.1 g (0.13 ml, 10 mmol) of triethylamine in 10 ml of acetonitrile was refluxed for 5 h. TLC analysis of the reaction mixture showed appearance of a new spot with R_f 0.86, whose size increased with time. Simultaneously, the spot with R_f 0.44 (lactam **IVc**) became smaller and disappeared in 3.5 h. After 5 h, the solvent was removed, the residue was ground with ether (3×10 ml), the precipitate was filtered off, and the solvent was distilled off. The residue was a yellow crystalline substance with mp 150–153°C (**Vc**).

REFERENCES

1. Topuzyan, V.O., Khachvankyan, G.Yu., Kurtikyan, T.S., Karapetyan, A.A., and Terzyan, S.S., *Russ. J. Org. Chem.*, 1997, vol. 33, no. 10, pp. 1457–1460.
2. Topuzyan, V.O., Akopyan, A.Z., Durgaryan, L.K., Vlasenko, E.V., Paronikyan, R.G., Paronikyan, R.V., and Ter-Zakharyan, Yu.Z., *Khim.-Farm. Zh.*, 1995, vol. 29, no. 3, pp. 42–44.
3. Krasovetskii, B.M., Lysova, I.V., and Afanasiadi, L.Sh., *Khim. Geterotsikl. Soedin.*, 1980, no. 7, pp. 909–911.