ISSN 1070-4272, Russian Journal of Applied Chemistry, 2009, Vol. 82, No. 4, pp. 605−612. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © V.P. Alyab'eva, N.V. Girbasova, A.Yu. Bilibi, 2009, published in Zhurnal Prikladnoi Khimii, 2009, Vol. 82, No. 4, pp. 612−618.

ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Different Approaches to Synthesis of *N*-Carboxyanhydrides of Amides of Trifunctional Amino Acids

V. P. Alyab'eva, N. V. Girbasova, and A. Yu. Bilibi

St. Petersburg State University, St. Petersburg, Russia

Received October 9, 2008

Abstract—Original method for synthesis of *N*-carboxyanhydrides of trifunctional α-amino acids containing substituents attached by amide bonds at the ω-functional group is suggested.

DOI: 10.1134/S1070427209040144

In recent decades, synthetic polymers whose structure includes various biological moieties, such as amino acids, saccharides, lipids, and immunogenic peptides [1–4], have been attracting the attention of chemists, biologists, and medics. This interest is due to the increasing demand (mainly for medical purposes) for biocompatible compounds with prescribed properties [5, 6]. A particular interest is associated with synthetic polymers whose macromolecules are fully composed of moieties of natural origin. Use of trifunctional amino acids opens up wide opportunities because both linear and branched structures can be constructed from these acids.

A polypeptide chain already bearing substituents can be formed by polycondensation of short peptide sequences [7]. Use of preliminarily synthesized dimers of γ-glutamic acid (GA) with residues of aspartic acid dimethyl ester, attached at the α-carboxy group, enabled the authors to synthesize oligomers with a degree of polymerization equal to 18–20 [8].

Another way is to polymerize substituted *N*-carboxyanhydrides (NCA). To advantages of this method belong the high degrees of polymerization and yield of polypeptides, purity of the polymers obtained, and nearly complete absence of racemization [9, 10]. As an example of application of this approach to synthesis of polyamino acids can serve communication [11] in which polymerization of α-amino acid NCAs bearing glycoside groups was described.

However, methods for synthesis of NCA compounds whose molecular structure contains an amide (peptide) bond (e.g., dipeptides) have not been developed, which restricts use of NCAs in synthesis of macromolecules with complex structure. The reason is that the aliphatic amide group readily enters into reactions with almost all reagents commonly used in NCA synthesis: thionyl chloride, phosphorus halides, and phosgene and its derivatives [12]. An almost only example of macromolecule synthesis by polymerization of NCAs containing aliphatic amide bonds in their structure was reported in [13]. It should be noted that NCAs were obtained using an unconventional low-active agent, dichloro(methoxy)methane, which was presumably due to a desire to protect the amide group from side reactions.

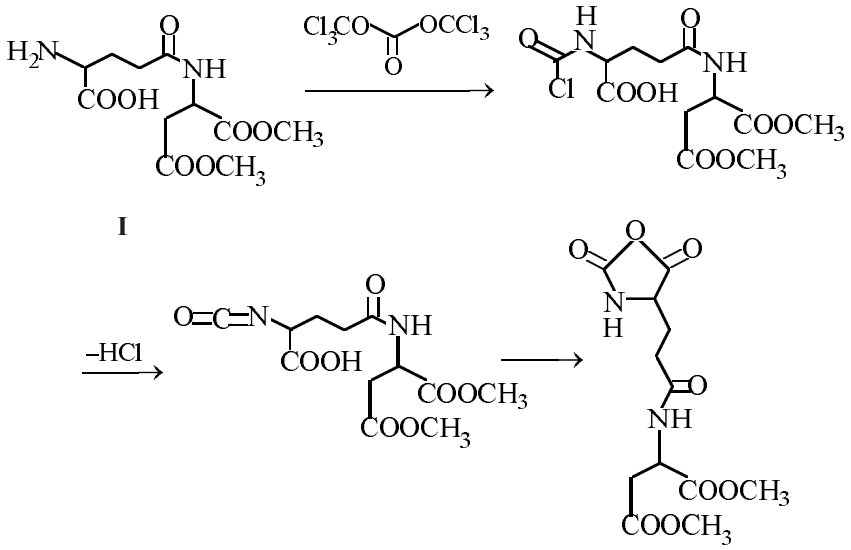
At present, an intensive search for methods that would preclude side reaction and enable use of less volatile, easily removable, and less toxic reagents [14].

In this study, methods for synthesis of NCA of L-glutamic acid (L-Glu) with branched substituents based on L-aspartic acid (L-Asp), attached by the amide bond at the γ-carboxy group. The main object of study was NCA of L-glutamic acid, with an L-Asp dimethyl ester as the substituent. Two approaches were used: with amino acid derivatives with free and protected amino groups.

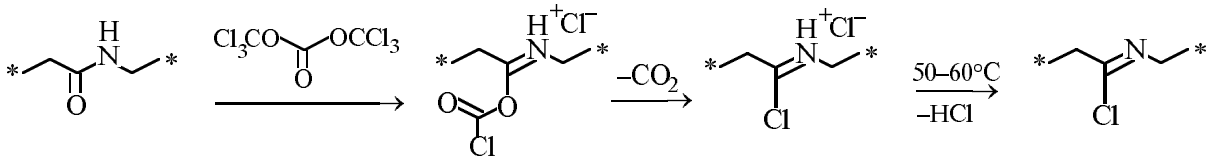
USE OF AMINO ACID DERIVATIVES WITH A FREE AMINO GROUP FOR NCA SYNTHESIS

As the starting compound served 2-amino-5-{[3-methoxy-1-(methoxycarbonyl)-3-oxo propyl]amino}-5-oxopentanic acid (**I**). NCA was synthesized by the standard procedure [15] with triphosgene in tetrahydrofuran (THF) at 60°C (synthesis 1). It was found that, under these conditions and also at lower temperatures, there

Scheme 1.



Scheme 2.



simultaneously occur the target reaction of NCA formation (1) [12] (Scheme 1) and addition of phosgene at the amide bond [16] (Scheme 2).

The formation of the chloroiminium salt was accompanied by the appearance of an intense yellow coloration of the solution. Heating of the reaction mixture yielded imidoyl halide.

According to ^{1}H NMR spectroscopic data, a noticeable decrease in the intensity of the NH signal of the amide group (δ = 5.60 ppm) was observed, together with the appearance of signals corresponding to the NCA structure [δ(CH)= 4.42 ppm, δ(NH) = 7.40 ppm]. Pure NCA could not be isolated from the mixture.

USE OF AMINO ACID DERIVATIVES WITH a *tert*-BUTYLOXYCARBONYL PROTECTION OF THE AMINO GROUP

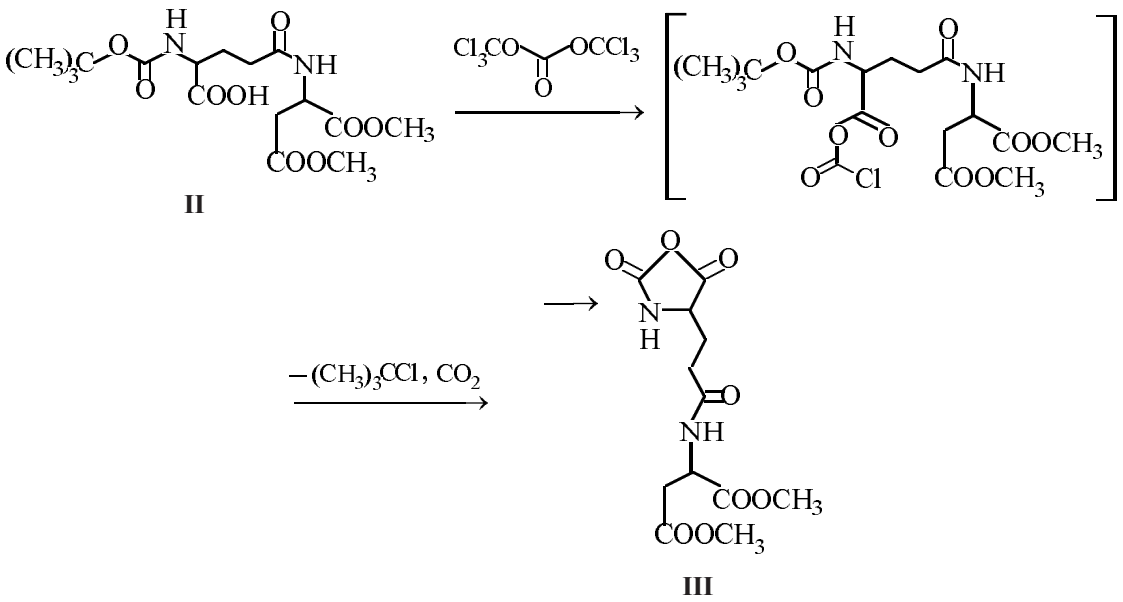
As the starting compound served 2-[(*tert*-butoxycarbonyl)amino]-5-{[3-methoxy-1-(methoxycarbonyl)-3-oxopropyl]amino}-5-oxopentanic acid (**II**).

Reaction of compound II with PBr_3 (synthesis 2). It is known [17] that NCA of glutamine can be synthesized by the reaction with PBr_3 in ether at 15–16°C. However, it was found, when reacting compound **II** with PBr_3 under similar conditions, that the signal of the proton of the amide group is absent in the ^{1}H NMR spectrum of the reaction mixture at all.

Reaction of compound II with triphosgene (synthesis 3). The formation of by-products could be minimized by using the data of the study [18], in which NCA was obtained from Boc-protected amino acid esters at room temperature, with the use of triphosgene and triethylamine (TEA). In this case, TEA catalyzed the formation of an intermediate. The reaction occurred at a high rate, because, immediately upon addition of TEA, nearly the whole amount of TEA hydrochloride (TEA HCl) precipitated from the ethyl acetate solution and was separated by filtration (Scheme 3).

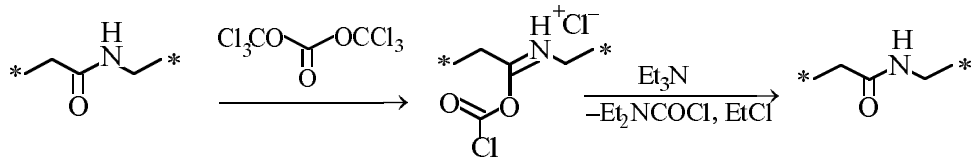
In contrast to the published technique, N-Boc amino acid was mixed with twofold, rather than equimolar, amounts of triphosgene (in terms of phosgene) and TEA. In doing so, it was assumed that one equivalent of phosgene was involved in the formation of NCA. The second equivalent of phosgene was consumed for a side reaction at the amide bond. The first equivalent of TEA was involved in the target reaction, and the second instantaneously decomposed the product formed upon

Scheme 3.



II **III**

Scheme 4.



phosgene addition to the amide bond [12] and precluded irreversible formation of the chloroiminium bond. It should be noted that the reaction of formation of the chloroiminium salt from the intermediate in ethyl acetate is so fast even at room temperature that it was necessary to add triethylamine to the reaction mixture immediately upon addition of the triphosgene solution (Scheme 4).

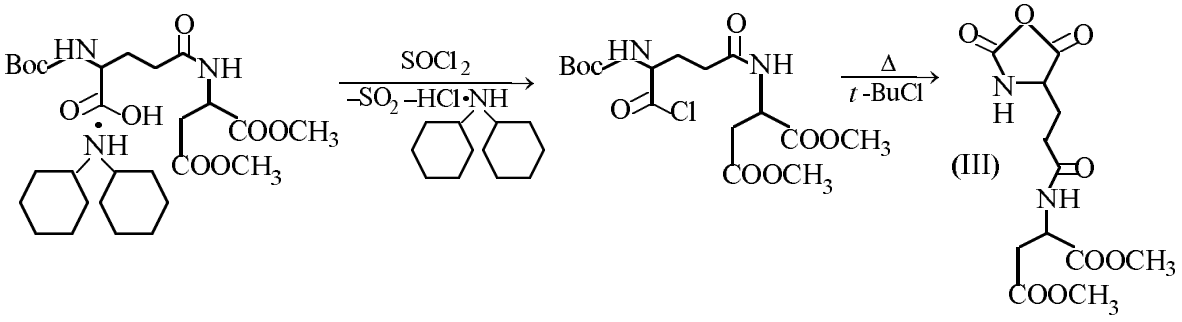
This approach made it possibly to nearly completely preclude occurrence of the reaction at the second reaction center. The reaction mixture contained up to 85–95% target product. Upon purification, methyl-3-(2,5-dioxo-1,3-oxasolan-4-yl)propanoate (**III**) was obtained in ~40% yield. According to the ^{1}H NMR spectrum, the substance contained no impurities except small amounts of TEA hydrochloride (about 5 mol %). In the spectrum of NCA, the intensity of the signal associated with NH protons of the amide bond remained unchanged. The signals of CH (δ = 4.30 ppm) and NH of the urethane group (δ = 5.63 ppm) disappeared and signals of CH (δ = 4.42 ppm) and NH (δ = 7.40 ppm) of the NCA ring appeared. The IR spectrum of the resulting product contained bands of stretching vibrations of C=O at 1860 and 1785 cm^{-1}, characteristic of NCA [18]. In addition, bands of stretching vibrations of C=O of ester groups (1735 cm^{-1}) and two bands of the amide group (Amide I, 1675 cm^{-1}; Amide II, 1600 cm^{-1}) were observed.

A significant disadvantage of this method is that the reagent is fixed at two reaction centers. As a result, the rate of TEA addition determined the ratio between products of the main and side reactions.

Another reagent frequently serving to synthesize NCA is thionyl chloride (TC). It is used in one of the oldest techniques for NCA synthesis, Leuchs method based on use of amino acids with benzyloxycarbonyl (*Z*-) protection of the amino group. The choice of just the *Boc*-group among protective groups of the urethane type was due to the fact that, in contrast to *Z*-protected amino acids, cyclization of *Boc*-protected amino acid haloanhydrides occurs even at temperatures higher than –30°C and they cannot be isolated [19, 20].

Reaction of compound II with TC in the presence of dimethylformamide (synthesis 4). It is known that catalytic amounts of DMFA accelerate the reaction of chloroanhydride formation [12]. In this case, dimethylformamidium chloride is the true chlorinating agent. With the use of a similar method [21],

Scheme 5.



chloroanhydride of a diacetyl derivative of 3,5-bis(4-aminophenoxy)benzoic acid was successfully obtained in the medium of *N*-methylpyrrolidone.

With an equimolar amount of TC in pure DMFA without heating, no chloroanhydride was obtained, and upon heating to 50–60°C in polar DMFA, HCl released in chloroanhydride formation removed the *Boc* protection. The ^{1}H NMR spectrum of the reaction mixture retained an unchanged signal of the NH proton of the amide bond, which indicated that no side reactions occurred. However, no signals of NCA protons were present in the spectrum. With the use of a preliminarily synthesized dimethylformamidium chloride in a mixture of solvents, ethyl acetate and DMFA, and with vacuum-degassing in the course of heating, approximately 10% NCA was formed in the reaction mixture, but the side reaction in which the *Boc*-protection was removed could not be completely eliminated.

Reaction of compound II with TC in the presence of pyridine (Py) (synthesis 5). There is published evidence that unstable chloroanhydrides have been obtained under mild conditions upon addition of a mole of Py per mole of TC [22]. The reaction was performed in ethyl acetate at room temperature with a twofold amount of Py, which not only catalyzed the process of chloroanhydride formation, but also bound the evolving HCl. A ^{1}H NMR spectrum of the reaction mixture demonstrated the formation of about 10% NCA. The presence of Py enabled preservation of the *Boc*-protection. However, partial occurrence of the reaction of TC with the amide bond could not be prevented.

Reaction a dicyclohexylammonium (DCHA) salt of compound II with TC (synthesis 6). The authors of the technique described in [23] demonstrated that DCHA salts of carboxylic acids are rapidly and quantitatively converted at room temperature to acyl chlorides in the reaction with a stoichiometric amount of TC. In this case, only a very weak racemization was observed. Previously, the reaction of the DCHA salt with TC has been successfully used to obtain acryloylaminobenzoic acid chloroanhydride [24], which could be synthesized in other ways.

In the present study, this reaction was employed to synthesize NCA. It was assumed that HCl released in the course of the reaction must be almost quantitatively bound with DCHA and can be easily removed from the reaction mixture in the form of the hydrochloride (Scheme 5).

A ^{1}H NMR spectrum of the reaction mixture demonstrated that 85–90% NCA is formed and there are no side reactions. NCA **III** was isolated by multiple reprecipitation from a THF–hexane mixture. The yield of pure NCA **III** was about 45%. The ^{1}H NMR spectrum fully coincided with that of NCA **III** obtained in the reaction with triphosgene.

In the yield of the target product, this method is comparable with that in which NCA is obtained with triphosgene and TEA, but is more convenient and reliable.

POLYMERIZATION OF NCA **III**

The effect of a solvent and initiator on the degree of polymerization was studied with NCA **III** formed from the DCHA salt without additional purification. In all cases, the anionic polymerization occurs, but its mechanisms vary with the initiator used [10, 25]. The polymerization was performed at a monomer : initiator ratio of 100 : 1, room temperature, and NCA concentration of 4% in the course of seven days. The viscosity of the resulting samples was measured in a non-helix-forming solvent, dichloroacetic acid (DCA). As in the case of numerous amino acid esters [9], the highest molecular

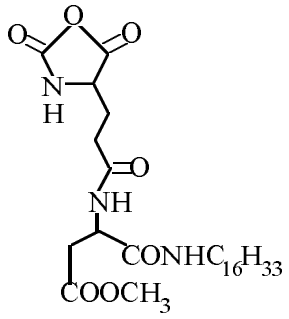
weight products are formed with TEA in chloroform and dioxane (Table 1).

The polymerization of a thoroughly purified NCA **III** was performed in the optimal solvent–initiator system (Table 1, sample no. 6) to give the polymer with the highest molecular weight.

It should be noted that hydrolysis of the ester groups of the resulting polymer by methods developed previously for other polymeric analogs [4, 8] can yield a polyamino acid bearing up to two carboxy groups per monomer unit.

SYNTHESIS AND POLYMERIZATION OF NCA CONTAINING TWO ALIPHATIC AMIDE BONDS AND A LONG ALIPHATIC MOIETY IN ITS STRUCTURE

A similar polymer with a clearly pronounced diphilic nature was synthesized with the role of a pendant substituent played by an aspartic acid derivative bearing a hexadecyl moiety at the α-carboxylic group. Such a compound was produced from aspartic acid β-methyl ester and hexadecylamine. The presence of an ester group means that polymers bearing both hydrophilic and hydrophobic groups in the side chain can be obtained. The structure of 3-(2,5-dioxo-1,3-oxasolan-4-yl)-*N*1-hexadecyl-propaneamide (**IV**) is shown below:



IV

The structure of the starting compound, 2-[(*tert*-butoxycarbonyl)amino]-5-({[(hexadecylamino)carbonyl]-3-methoxy-3-oxopropyl}amino)-5-oxopentanic acid (**V**), contains two aliphatic amide bonds. NCA (**IV**) was synthesized by the technique developed in this study (synthesis 6). The ^{1}H NMR spectrum of the reaction mixture demonstrated a nearly quantitative formation of NCA. NCA (**IV**) was purified by reprecipitation from THF–hexane and ethyl acetate–hexane mixtures. The yield of pure NCA (**IV**) was about 80%. The ^{1}H NMR spectrum of NCA (**IV**) contained unchanged signals of NH protons of the amide bonds. The CH (δ = 3.8 ppm) and NH (δ = 5.72 ppm) signals of the urethane group disappeared and the CH (δ = 4.40 ppm) and NH (δ = 7.23 ppm) signals of the NCA ring appeared.

Table 1. Results of NCA (III) polymerization

Sample no.	Solvent	Initiator	$[\eta]_{DCA}^{25°C}$, dl g^{-1}
1	Chloroform	TEA	0.16
2	Dioxane	TEA	0.14
3	DMFA	TEA	0.06
4	Dioxane	MeONa	0.11
5	"	Butylamine	0.06
6	Chloroform	TEA	0.25

It should be noted that the amount of *N*-carboxyanhydrides formed in the reaction mixture (80–100%) depends on the purity of the starting compounds (compound **II**) could be purified to completely remove trace amounts of isomeric 4-[(*tert*-butoxycarbonyl)-amino]-5-{{3-methoxy-1-(methoxycarbonyl)-3-oxopropyl]amino}-5-oxopentanic acid) and on the hygroscopicity of the NCA themselves [compound **IV** is less hygroscopic than **III** because of the presence of a hydrophobic moiety].

The polymerization of NCA **IV** was performed in solutions of dioxane and a 1 : 2 mixture of methylene chloride and DMFA under the conditions developed. The choice of the solvent is due to the solubility of the monomer. The viscosity of the polymer **VI** samples obtained was measured in DAC at 25°C. Since the observed polyelectrolyte effect, which may be due to protonation of the amide bonds of DAC, the characteristic viscosity of the samples under study could not be determined. The viscosities were compared at a concentration of 0.74 g dl^{-1}, which was in the linear part of the dependence η_r–c for both samples (Table 2).

EXPERIMENTAL

The starting compounds were synthesized from L-Asp and L-Glu of pure grade. The solvents were purified by the standard methods [26]. The NMR spectra were measured on a DPX 300 instrument in $CDCl_3$ and DMSO-d_6 solutions, and the IR spectra, on a Specord 75 IR instrument in chloroform solutions (c = 0.4 g/100 ml). The viscosities were measured with an Ubbelohde

Table 2. Reduced viscosity η_r of polymer **VI** (c = 0.74 g dl^{-1}, DAC, 25°C)

Polymerization medium	η_r
Dioxane	0.15
Methylene chloride–DMFA	0.20

viscometer. The starting compounds were synthesized by the methods described in [27, 28].

Synthesis of NCA III with the use of triphosgene (synthesis 3). To a solution of 0.32 g (0.817 mmol) of compound **II** in 7 ml of ethyl acetate was added, in the atmosphere of argon, 0.143 g (0.545 mmol or 2/3 of an equivalent) triphosgene in 2.5 ml of ethyl acetate. To the reaction mixture was immediately added 0.23 ml (1.634 mmol or 2 equivalents) of TEA in 0.6 ml of ethyl acetate. A massive precipitation of TEA hydrochloride was observed. The mixture was agitated for several hours at room temperature and then allowed to stand overnight. The gaseous reaction products were removed with a flow of argon in the course of 0.5 h. The precipitated TEA hydrochloride was filtered off. A 2/3 part of ethyl acetate was removed in a water-jet pump vacuum. The concentrated solution was allowed to stand overnight in a freezing chamber. The additionally formed TEA salt precipitate was filtered off. The solvent was completely removed. The product was several times reprecipitated from methylene chloride into ether. Residual amounts of the solvents were removed in an oil pump vacuum. Yield: 0.1 g (40%) mp 63–65°C. ^{1}H NMR spectrum, $CDCL_3$, δ, ppm: 2.13, 2.34 [both m, 1H, C**H**$_2$–CH$_2$–C(O)]; 2.53 [m, 2H, CH$_2$–C**H**$_2$–C(O)]; 2.9 (m, 2H, –**CH**$_2$–), 3.72, 3.79 [both s, 3H, C(O)-OC**H**$_3$]; 4.42 (m, 1H, C**H**$_{NCA}$); 4.88 (m, C**H**–NH–C(O)–CH$_2$); 7.00 [d, 1H, N**H**–C(O)–O, J^3 = 7.26]; 7.40 (s, 1H, N**H**$_{NCA}$). According to the spectrum, the product also contains trace amounts of $Et_3N \cdot HCl$: 1.9 (m), 3.12 (m).

Synthesis of NCA III from the DCHA salt (synthesis 6). NCA was synthesized in an anhydrous medium, with the system bubbled with dried argon. $SOCl_2$ was distilled over linseed oil to remove SO_2 and HCl formed in its decomposition was used the same day. To a solution of 0.695 g (1.216 mmol) of the DCHA salt in 7 ml of ethyl acetate was rapidly added, at 28–30°C and vigorous agitation, a solution of 0.145 g (1.216 mmol) of TC in 2.5 ml of the same solvent. The reaction mixture was allowed to stand under agitation in the atmosphere of Ar for 5 h and then DCHA hydrochloride was filtered off. After that the solution was concentrated threefold, activated carbon was added, and the mixture was agitated for 30 min to remove colored impurities. The carbon was filtered off, the solvent was removed in a vacuum, and the residue was several times thoroughly ground with absolute diethyl ether and dried in an oil pump vacuum. Then multiple reprecipitation from a mixture of tetrahydrofuran and *n*-hexane was performed. The oily product was ground in hexane and dried in an oil pump vacuum. Yield: 0.173 g (45%), mp 63–65°C. PMR spectrum ($CDCl_3$), δ, ppm: 2.13, 2.25 [both m, 1H, C**H**$_2$–CH$_2$–C(O)]; 2.50 [m, 2H, CH$_2$–C**H**$_2$–C(O)]; 2.95 (m, 2H, –**CH**$_2$–); 3.66, 3.75 [both s, 3H, C(O)–OC**H**$_3$]; 4.45 (m, 1H, C**H**$_{NCA}$); 4.88 [m, C**H**–NH–C(O)–CH$_2$]; 7.18 [d, 1H, N**H**–C(O)–O]; 7.50 (s, 1H, N**H**$_{NCA}$).

Polymerization of NCA (III). THE polymerization was performed in chloroform, dioxane, and DMFA at a monomer : initiator ratio of 100 : 1, room temperature, and NCA concentration of 4% in the course of seven days in a light-protected place. TEA, sodium methylate, or butylamine served as an initiator. The formation of the polymer was judged by TLC from disappearance of the NCA spot. The polymer was isolated by precipitation into methanol (or into methyl acetate in the case of synthesis in DMFA). The purification was carried out by reprecipitation from chloroform into methanol, the precipitated polymer was washed with hexane and dried in an oil-pump vacuum. Yield of the polymer about 100%, mp (sample no. 2) 127–132°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.79–2.7 [4H, C**H**$_2$–CH$_2$–C(O)], 2.72–3.2 (C**H**$_2$), 3.56–3.87 [6H, C(O)–OC**H**$_3$], 3.92–4.22 {1H, –[C**H**–NH–C(O)]$_n$–}, 3.72–5.01 (C**H**), 7.11–7.52 (N**H**), 8.12–8.54 {1H, –[CH–N**H**–C(O)]$_n$–}.

IR spectrum (4% solution in chloroform): 1650 cm^{-1} (C=O vibrations of amide bonds in the backbone and side chain), Amide **II** at 1600 cm^{-1} and broad band of Amide **II** at 1530 cm^{-1}. The band broadening in the IR spectrum may be also due to presence of free and hydrogen-bound C=O and NH groups.

Synthesis of NCA IV. The reaction was performed by the procedure used in synthesis 6. The reaction mixture was treated in 1 h. The precipitate formed was filtered off, suspended in THF, and agitated at room temperature for 30 min. The insoluble DCHA salt was filtered off. Then the equal volume of hexane was added to the filtrate and the mixture was allowed to stand overnight in a refrigerator. The NCA precipitate was filtered off and dried in a vacuum over P_2O_5. The reaction mixture

was concentrated to dryness and dissolved in a minimum amount of ethyl acetate, and then hexane was added in a ratio of approximately 4 : 1). The NCA precipitate was filtered off and dried in a vacuum over P_2O_5. The total yield: 80%, mp 137–139°C. Calculated (%) C 61.8; H 8.84; N 8.00. $C_{27}H_{46}N_3O_7$. Found (%): C 62.03, 61.68; H 9.06, 9.03; N 7.81, 7.85. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.91 (t, 3H, C**H**$_3$); 1.21–1.33 [m, 24H, (C**H**$_2$)$_{12}$]; 1.51 [m, 2H, C**H**$_2$(CH$_2$)$_{12}$]; 1.66 [m, 2H, C**H**$_2$(CH$_2$)$_{13}$]; 2.12, 2.34 [both m, 1H, C**H**$_2$–CH$_2$–C(O)]; 2.52 [m, 2H, CH$_2$C**H**$_2$–C(O)]; 2.63–2.95 [m, 2H, C**H**$_2$–C(O)–O]; 3.24 (m, 2H, C**H**$_2$NH); 3.75 (s, 3H, OC**H**$_3$); 4.40 (m, 1H, C**H**$_{NCA}$); 4.75 [m, C**H**–NH–C(O)–CH$_2$]; 6.65 (m, 1H, C**H**$_2$NH); 7.17 [d, 1H, N**H**–C(O)–O, J^3 = 7.24]; 7.23 (s, 1H, N**H**$_{NCA}$).

Polymerization of NCA IV. The polymer was synthesized at an NCA concentration of 4%, monomer : initiator (TEA) ratio of 100 : 1, and room temperature in the dark in the course of seven days. Dioxane and a 1 : 2 mixture of methylene chloride and DMFA were used as solvents. Yield: 63% (dioxane) and 65% (methylene chloride–DMFA), mp of both samples 243–246°C (with degradation). ^{1}H NMR spectrum ($CDCl_3$, DMSO-d_6), δ, ppm: 1.45 (s, 3H, C**H**$_3$), 0.8–1.5 [2*n*H, (C**H**$_2$)$_n$], 2.00–2.35 (m, 2H, C**H**$_{2hexd}$), 2.34–3.20 [m, 2H, C**H**$_2$C**H**$_2$–C(O)], 3.00–3.71 [2H, C**H**$_2$–C(O)–O]; 3.20–3.35 (2H, C**H**$_{2hexd}$); 4.25 (s, 3H, OC**H**$_3$); 5.27–5.50 [1H, NH–C**H**–C(O)]. Polymer **VI** shows a pronounced tendency toward aggregation and a low solubility. It is well dissolved only in dichloroacetic and trifluoroacetic acids, and also in cyclohexanol under heating.

CONCLUSIONS

(1) A method for obtaining *N*-carboxyanhydrides of compounds containing amide bonds in their molecular structure under mild conditions was developed. This method makes it possible to preclude occurrence of side reactions.

(2) It was shown that *N*-carboxyanhydrides of compounds containing bulky substituents in their structure are capable of polymerization to give oligomers.

ACKNOWLEDGMENTS

The study was financially supported by the Russian Foundation for Basic Research (project no. 06-03-3292a) and by a grant from Prof. A de Meijere (University of Gцttingen, Germany).

REFERENCES

1. Zistler, A., Koch, S., and Schluter, A.D., *J. Chem. Soc., Perkin Trans.*, 1999, vol. 1, pp. 501–508.
2. Deng, H.-T., Xu, Z.-K., Wu, J., et al., *J. Mol. Catal. B: Ensymatic*, 2004, vol. 28, pp. 95–100.
3. Cloninger, M.J., *Current Opinion Chem. Biol.,* 2002, vol. 6, pp. 742–748.
4. Girbasova, N.V., Migunova, I.I., Raspopova, I.R., and Bilibin, A.Yu., *Vysokomol. Soedin., Ser. A*, 2003, vol. 45, no. 4, pp. 550–561.
5. Sadler, K. and Tam, J.P., *Rev. Mol. Biotechnol*., 2002, vol. 90, pp. 195–229.
6. Veprek, P. and Jezek, J., *J. Peptide Sci*., 1999, vol. 5, pp. 5–23.
7. Sanda, F., Fujiyama, T., and Endo, T., *J. Polym. Sci., Part A*, 2001, vol. 39, pp. 732–741.
8. Alyab'eva, V.P., Girbasova, N.V., and Bilibin, A.Yu., *Vestn. SPb, Gos. Univ.*, 2006, Ser. 4, issue 3, pp. 95–105.
9. Karnup, A.S., Uverskii, V.N., and Medvedkin, V.N., *Bioorgan. Khim*., 1996, vol. 22, no. 8, pp. 563–574.
10. Deming, T.J., *Adv. Drug Delivery Rev.,* 2002, vol. 54, pp. 1145–1155.
11. Aoi, K., Tsutsumiuchi, K., and Okada, M., *Macromolecules*, 1994, vol. 27, pp. 875–877.
12. *Obshchaya organicheskaya khimiya* (General Organic Chemistry), vol. 3, Kochetkov, N.K., Ed., Moscow: Khimiya, 1982.
13. Yu, M., Novak, A.P., and Deming, T.J., *J. Am. Chem. Soc*., 1999, vol. 121, pp. 12210–12211.
14. Fujita, Y., Koga, K., Kim, H.-K., et al., *J. Polym. Sci., Part A*, 2007, vol. 45. 5365–5369.
15. Daly, W.H. and Poshй, D., *Tetrahedron Lett.,* 1988, vol. 29, no. 46, pp. 5859–5842.
16. *Obshchaya organicheskaya khimiya* (General Organic Chemistry), vol. 4, Kochetkov, N.K., Ed., Moscow: Khimiya, 1983.
17. Hirschmann, R., Schwam, H., Strachan, R.G., et al., *J. Am. Chem. Soc*., 1971, vol. 93, no. 10, pp. 2746–2754.
18. Wilder, R. and Mobashery, Sh., *J. Org. Chem*., 1992, vol. 57, pp. 2755–2756.
19. Carpino, L.A., Beyermann, M., Wenschuh, H., and Bienert, M., *Acc. Chem. Res*., 1996, vol. 29, pp. 268–274.
20. Losse, G. and Wehrstedt, K.D., *Z. Chem*., 1981, vol. 121, p. 148.

21. Ueda, M., Washio, I., and Shibasaki, Y., Abstracts of Papers, *40th Int. Macromol. Symp., Paris*, France, July. 2004.

22. *Weygand-Hilgetag Organisch-chemische Experimentierkunst*, Hilgetag, G. and Martini, A., Eds., Leipzig: Johann Ambrosius Barth, 1964, 3rd ed.

23. Matsuda, F., Iton, Sh., Hatfori, N., et al., *Tetrahedron*, 1985, vol. 41, no. 18, pp. 3625–3631.

24. Bilibin, A.Yu., Girbasova, N.V., Matsuk, A.V., et al., *Vysokomol. Soedin., Ser. A,* 2007, vol. 49, no. 4, pp. 581–592.

25. Goodman, M. and Peggion, E., *Pure Appl. Chem*., 1981, vol. 53, pp. 699–714.

26. Gordon, A.J. and Ford, R.A., *The Chemist's Companion*, New York: Wiley, 1972.

27. Ramalingam, K. and Woodard, R.W., *J. Org. Chem*., 1988, vol. 53, pp. 1900–1903.

28. Gershkovich, A.A. and Kibirev, V.K., *Sintez peptidov: Reagenty i metody* (Synthesis of Peptides: Reagents and Methods), Kiev: Naukova dumka. 1987.