Synthesis of *N*-(amidomethyl)- and *N*-(imidomethyl)-α-amino acid esters by reactions of α-amino acid esters with formaldehyde and amides or imides

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Reactions of hydrochlorides of glycine, alanine, phenylalanine, L-isoleucine, and L-valine esters with aromatic and heteroaromatic carboxamides afforded hydrochlorides of the corresponding *N*-(amidomethyl)-α-amino acid esters. *N*-(Phthalimidomethyl)-α-amino acid esters were obtained by reactions of α-amino acid esters containing free amino groups with formaldehyde and phthalimide. The ^{1}H NMR studies demonstrated that the chiral centers of α-amino acids may be retained in the course of condensation. Reactions of the Mannich bases obtained and their hydrochlorides with acetic anhydride and tosyl chloride afforded the corresponding *N*-acyl and *N*-sulfonyl derivatives.

Key words: glycine, alanine, phenylalanine, L-isoleucine, L-valine, formaldehyde, amides, phthalimide, dimethylformamide, acetic anhydride, tosyl chloride, condensation, Mannich reaction.

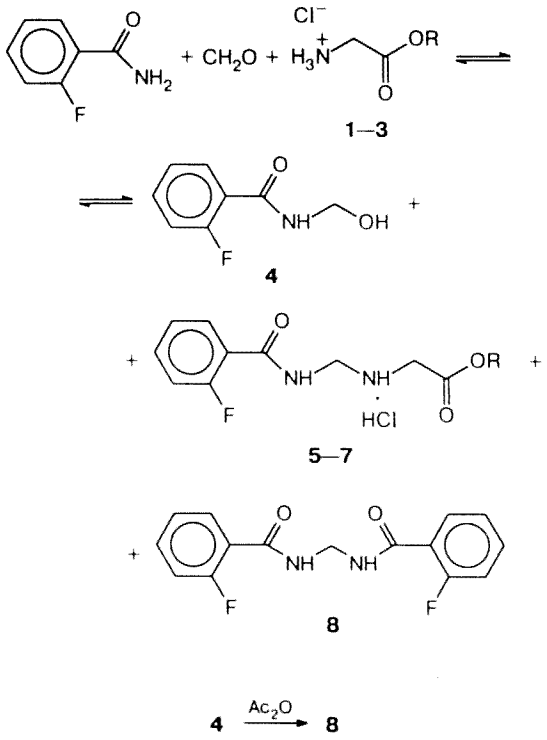
Previously, we have reported the synthesis of *N*-(amidomethyl)- and *N*-(imidomethyl)glycine esters starting from glycine esters, amides or imides of dicarboxylic acids, and formaldehyde.[1–3] The compounds obtained are derivatives of *N*-(amidomethyl)-α-amino acids, whose representatives exhibit antibacterial activity.[4]

However, our attempts to synthesize the products of the condensation of glycine esters or their hydrochlorides with formaldehyde and *ortho*-substituted benzamides or hetarylamides have not met with success. We failed also to prepare the Mannich adducts by reactions of alanine and phenylalanine esters with benzamide or *para*-substituted benzamides.

With the aim of finding the conditions that make possible reactions of esters of different α-amino acids with arylamides, we studied the reactions of glycine ester hydrochlorides (**1**—**3**) with formaldehyde and *o*-fluorobenzamide (Table 1). Dioxane, Pr^{i}OH, toluene, DMF, and DMSO were used as solvents. A 29% aqueous solution of formaldehyde and anhydrous paraformaldehyde were used as sources of formaldehyde. Reactions were carried out in the presence of acids and bases or without catalysts. Reactions proceeded over 12 h (a further increase in the reaction time did not lead to any change in the ratio of the products). The compositions of the crystalline condensation products isolated from the reaction mixtures were determined by ^{1}H NMR and TLC methods.

Apparently, the reaction is in equilibrium (see Scheme 1). In most cases, the condensate is a mixture of the initial glycine ester (**1**—**3**), *N*-hydroxymethyl-*o*-fluorobenzamide (**4**), and *N*-(amidomethyl)glycine ester hydrochloride (**5**—**7**). Compounds **1**—**3** and **5**—**7**

Scheme 1



R = Me (**1**, **5**), Et (**2**, **6**), CH_2Ph (**3**, **7**)

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 7, pp. 1761—1769, July, 1996.

Table 1. Composition of the reaction mixture and the yields of the products of the reaction of glycine ester hydrochlorides (**1**—**3**) with *o*-fluorobenzamide and formaldehyde under different conditions

Glycine ester	Solvent	Source CH_2O[a]	Catalyst	Composition of the reaction mixture (%)			Yield of **5**—**7** (%)
				1—**3**	**4**	**5**—**7**	
1	Pr^{i}OH	A	—	50[b]	0	**5**, 0	0
1	Pr^{i}OH	A	AcONa	51	0	**5**, 49	14[c]
2	Pr^{i}OH	A	AcONa	83	0	**6**, 17	3[c]
2	Dioxane	A	—	57	0	**6**, 43	8
1	DMSO	A	—	22	8	**5**, 70	37
2	DMSO	A	—	10	17	**6**, 71	17
2	DMF	A	—	31	14	**6**, 55	29
1	DMSO	B	TsOH	23	6	**5**, 71	38
1	DMF	B	TsOH	0	0	**5**, 100	88
3	DMF	B	TsOH	7	0	**7**, 93	66

[a] A is a 29% aqueous solution and B is $(CH_2O)_n$. [b] The initial *o*-fluorobenzamide was the second component of the reaction mixture. [c] The crystalline product was obtained by treating the reaction mixture with HCl.

were isolated as individual compounds by fractional crystallization and TLC and were identified by IR and NMR spectroscopy (compounds **1**—**3** were identified also from the absence of depression of melting points of mixtures containing known samples).

Amide **4** was obtained as a mixture with *o*-fluorobenzamide formed from **4** under the conditions of TLC on Silica gel. The structure of **4** was confirmed by conversion of this compound to *N*,*N*′-bis(*o*-fluorobenzamido)methane (**8**) under the action of acetic anhydride; compound **8** is a typical product of the reactions of aromatic *N*-hydroxymethylcarboxamides with acetic anhydride in the absence of a solvent.[5]

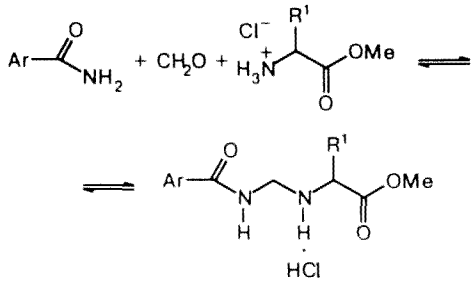
We succeeded in shifting the equilibrium toward the formation of *N*-(amidomethyl)glycine ester hydrochlorides **5**—**7** by using anhydrous paraformaldehyde and performing the reaction in dipolar aprotic solvents in the presence of catalytic amounts of TsOH. Apparently, the function of the catalyst is to protonate and then to dehydrate *N*-hydroxymethyl-*o*-fluorobenzamide **4** to the immonium cation, which reacts with glycine ester hydrochloride. The fact that compound **8** was isolated when the reaction was carried out in boiling toluene in the presence of sulfuric acid supports this suggestion.

The results of the reaction are scarcely affected by the nature of the alkoxycarbonyl group R of the glycine ester. The reactions with the hydrochlorides of methyl, ethyl, and benzyl esters of glycine gave comparable yields of adducts **5**—**7** under the conditions studied.

The regularities found were used for the synthesis of the analogous products of condensation with esters of a series of α-amino acids, including enantiomerically pure acids, and aromatic and heterocyclic carboxamides.

The reactions were carried out with anhydrous paraformaldehyde in dimethylformamide in the presence of TsOH. Reactions afforded hydrochlorides of esters of *N*-(amidomethyl)glycine, *N*-(amidomethyl)alanine, *N*-(amidomethyl)phenylalanine, *N*-(amidomethyl)-L-valine, and *N*-(amidomethyl)-L-isoleucine (**9**—**13**, **15**, and **16**) in 21—65 % yields (see Scheme 2, Table 2). Compound **14** was converted without isolation to the corresponding acetyl derivative (see Scheme 5 below).

Scheme 2



9—**16**

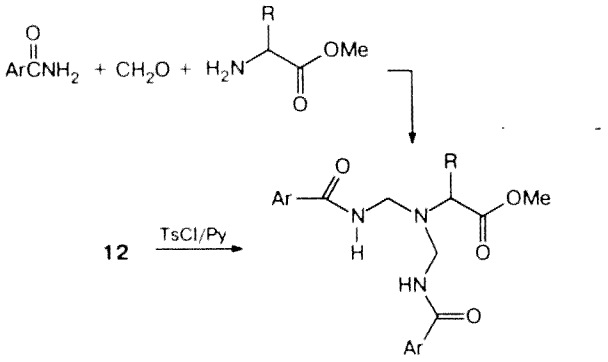
9—**12**: Ar = *p*-$NO_2C_6H_4$, R^1 = Me (**9**), CH_2Ph (**10**), L-CH(Me)$_2$ (**11**), L-CH(Me)Et (**12**)
13: Ar = *p*-BrC_6H_4, R^1 = Me
14: Ar = *o*-OHC_6H_4, R^1 = H
15: Ar = 3,5-dichloroisothiazolyl-4, R^1 = H
16: Ar = 3-pyridyl

Table 2. Composition of the reaction mixture and the yields of the products (**9**—**16**) of the reaction of α-amino acid ester hydrochlorides with aryl(hetaryl)amides and paraformaldehyde in dimethylformamide at 20 °C in the presence of TsOH

Compound	Composition of the reaction mixture (%)		Yield **9**—**16** (%)
	α-Amino acid ester hydrochloride	Compound (**9**—**16**)	
9	0	100	65
10	7	93	45
11	12	88	21
12	3	97	52
13	2	98	33
14	41	59	41
15	7	93	46
16	5	95	26

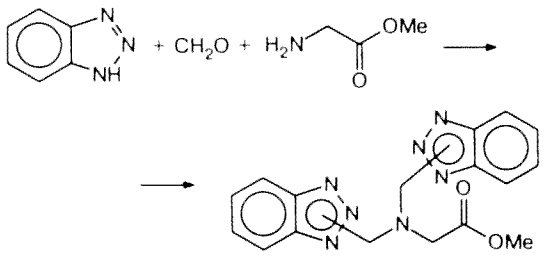
Reactions of α-amino acid esters containing a free amino group with formaldehyde and aromatic (heteroaromatic) carboxamides proceed in different ways, apparently due to the fact that conversions involving a second H atom of the amino group may occur. In specific cases, we succeeded in shifting the equilibrium toward the formation of compounds containing two amidomethyl substituents at the N atom of amino acid as the major products. Thus, the reaction of a molar equivalent of glycine methyl ester with two equivalents of formaldehyde and *p*-bromobenzamide afforded crystalline *N*,*N*-bis(*p*-bromobenzamidomethyl)glycine methyl ester (**17**). The analogous product (**18**) was unexpectedly obtained along with *N*-(*p*-nitrobenzamidomethyl)-L-isoleucine methyl ester (**31**) when hydrochloride **12** was treated with tosyl chloride in pyridine. Apparently, the formation of **18** is indicative of the dissociation of **12** with the cleavage of the C—N bond under the reaction conditions.

Scheme 3



17: R = H; Ar = *p*-BrC_6H_4;
18: R = CH(Me)Et; Ar = *p*-$NO_2C_6H_4$

Other types of compounds containing an NH group can also undergo these transformations, as was demonstrated by the synthesis of *N*,*N*-bis(benzotriazolylmethyl)glycine methyl ester (**19**) from glycine methyl ester, benzotriazole, and formaldehyde.



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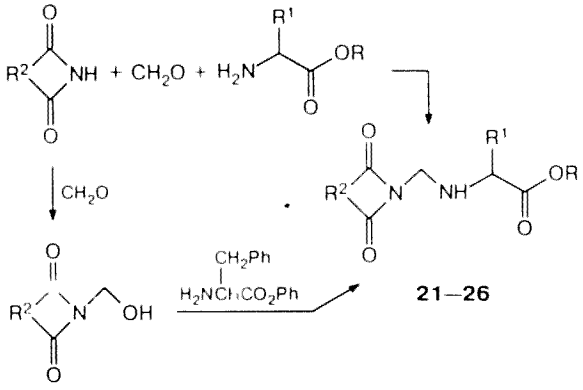
Whereas the synthesis of *N*-(amidomethyl)-α-amino acid esters called for a search for special reaction conditions (dimethylformamide, paraformaldehyde, or TsOH), the conditions that we used previously for the preparation of *N*-(imidomethyl)glycine esters[2] appeared to be suitable for the synthesis of *N*-(imidomethyl)-α-amino acid esters. Thus, imides of succinic and *o*-phthalic acids enter into three-component reactions with alanine, phenylalanine, L-valine, and L-isoleucine esters and formaldehyde in Pr^iOH (see Scheme 4) to yield *N*-(imidomethyl)-α-amino acid esters **21**—**26** (Table 3).

Scheme 4



20

	R	R^1	R^2
21:	Et	CH_2Ph	$(CH_2)_2$
22:	Me	Me	C_6H_4-*o*
23:	Et	Me	C_6H_4-*o*
24:	Et	CH_2Ph	C_6H_4-*o*
25:	Me	$CHMe_2$	C_6H_4-*o*
26:	Me	CH(Me)Et	C_6H_4-*o*

Compounds **21** and **24** were isolated from the reaction mixture as individual compounds. The oily condensation products **22**, **25**, and **26** were transformed into crystalline hydrochlorides by careful treatment with HCl in $CHCl_3$; compound **23** was transformed into the corresponding *N*-acyl derivative.

The synthesis of **21**—**26** involves, apparently, the stage of formation of *N*-hydroxymethylimides. Actually, the reaction of *N*-hydroxymethylphthalimide **20** with phenylalanine ethyl ester afforded ester **24** in a yield of 43 %.

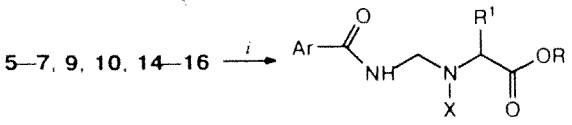
The structures of *N*-(amidomethyl)- and *N*-(imidomethyl)-α-amino acid esters and their hydrochlorides were established by IR and NMR spectroscopy (Tables 3 and 4). Most of these adducts are unstable in solutions, which made it impossible to isolate them in an analytically pure form.

With the aim of identifying hydrochlorides **9**—**12** and **27** (the last mentioned compound has been synthesized previously[1]), these compounds were transformed into the more stable free bases (**28**—**32**) (Tables 5 and 6).

Table 3. Yields, melting points, and the IR and ^{1}H NMR data of *N*-(imidomethyl)-α-amino acid esters **(21—26)**

Compound	Yield (%)	M.p. /°C	IR, ν/cm^{-1}		^{1}H NMR, δ (*J*/Hz)				
			C=O	NH	R^1	R^2	R	NCH_2N	NCHC
21	55	81—84	1700, 1716, 1728, 1768	3344	2.82 (dd, 1 H, CH_2, J_1 = 12.8, J_2 = 8.0), 2.97 (dd, 1 H, CH_2, J_1 = 12.8, J_2 = 5.0), 7.15 (d, 2 H, Ph, J = 7.0), 7.71—7.82 (m, 3 H, Ph)	2.57 (s, 4 H, 2 CH_2)	1.20 (t, 3 H, Me), 4.08 (q, 2 H, OCH_2)	4.43 (dd, J_1 = 20.5, J_2 = 13.5)	3.62 (t, 7.3)
22 · HCl	54	133—137	1730, 1750, 1790	2400—2800, 2980	1.53 (d, 3 H, Me, J = 6.5)	7.85—8.05 (m, 4 H, Ar)	3.72 (s, 3 H, Me)	4.87 (dd, J_1 = 17.0, J_2 = 13.0)	4.23 (q, 6.5)
24	50	83—86	1710, 1730, 1775	3345—3350	2.86 (dd, 1 H, CH_2, J_1 = 13.0, J_2 = 7.2), 2.97 (dd, 1 H, CH_2, J_1 = 13.0, J_2 = 5.9), 7.09—7.25 (m, 5 H, Ph)	7.80—7.88 (m, 2 H, Ar), 7.67—7.75 (m, 2 H, Ar)	1.03 (t, 3 H, Me), 3.85 (q, 2 H, OCH_2)	4.65 (dd, J_1 = 19.7, J_2 = 13.0)	3.68 (t, 7.3)
25·HCl	41	126—130	1720, 1755, 1785	2620—2900, 2980—3060	0.90 (d, 3 H, Me, J = 6.7), 1.00 (d, 3 H, Me, J = 6.7), 2.25—2.40 (m, 1 H, CH)	7.83—8.05 (m, 4 H, Ar)	3.65 (s, 3 H, Me)	4.77 (dd, J_1 = 18.0, J_2 = 13.0)	3.96 (d, 2.5)
26·HCl	58	125—129	1730, 1750, 1790	2400—3000	0.76—1.00 (m, 6 H, Me), 1.25 (m, 1 H; CH_2), 1.47 (m, 1 H, CH_2), 2.00—2.18 (m, 1 H, CH)	7.80—8.00 (m, 4 H, Ar)	3.65 (s, 3 H, Me)	4.79 (dd, J_1 = 19.0, J_2 = 12.0)	4.01 (d, 2.0)

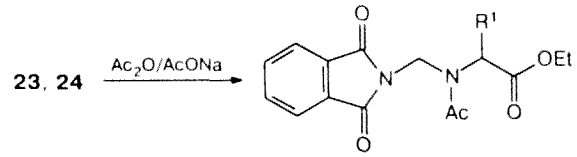
Scheme 5



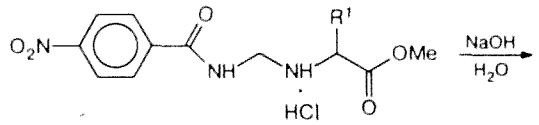
33—41

i. Ac_2O/AcONa or TsCl/Py

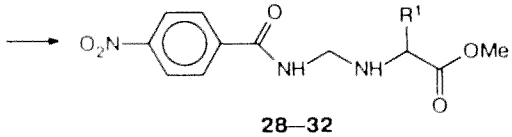
Compound	R	R^1	Ar	X
33	Me	H	$C_6H_4F(o)$	Ac
34	Et	H	$C_6H_4F(o)$	Ac
35	CH_2Ph	H	$C_6H_4F(o)$	Ac
36	Me	Me	$C_6H_4NO_2(p)$	Ac
37	Me	CH_2Ph	$C_6H_4NO_2(p)$	Ac
38	Me	H	$C_6H_4OAc(o)$	Ac
39	Me	H	3-Piridyl	Ac
40	Me	H	$C_6H_4F(o)$	Ts
41	Me	H	3,5-Dichloroisothiazolyl-4	Ts



42: R^1 = Me
43: R^1 = CH_2Ph



9—12, 27



28—32

R^1 = Me (**9**, **28**); CH_2Ph (**10**, **29**); $CH(Me)_2$ (**11**, **30**); CH(Me)Et (**12**, **31**); H (**27**, **32**)

The structures of compounds **5—7**, **9**, **10**, **14—16**, **23**, and **24** were additionally confirmed by conversions of these compounds to the corresponding *N*-acetyl and *N*-tosyl derivatives (**33—43**) by reactions with acetic anhydride in the presence of AcONa or with tosyl chloride in pyridine (Scheme 5, Tables 7 and 8).* Un-

* When *N*-(α-salicylamidomethyl)glycine methyl ester hydrochloride (**14**) reacts with acetic anhydride, acylation of the hydroxyl group at the aromatic nucleus occurs along with acylation of the amino group.

Table 4. Melting points and the data of the IR and ^{1}H NMR spectra of *N*-(amidomethyl)-α-amino acid ester hydrochlorides **(5—7 and 9—16)**

Compound	M.p. /°C	IR, ν/cm^{-1}			^{1}H NMR, δ (*J*/Hz)					
		C=O	NH	NO_2	Ar (*o*-FC_6H_4)*	R^1	NCH_2N	NCHC (NCH_2C)*	R (Me)**	NH
5	135—139	1615, 1665, 1750	2620—2800, 2880—2960, 3300	—	7.25—7.39 (m, 2 H), 7.60 (q, 1 H, *J* = 6.5), 7.75 (t, 1 H, *J* = 7.5)	—	4.63 (d, *J* = 7.6)	4.00 (s, 2 H)	3.72 (s, 3 H, Me)	9.28 (t, *J* = 7.6)
6	117—121	1620, 1670, 1750	2620, 3020, 3240	—	7.29—7.45 (m, 2 H), 7.41 (q, 1 H, *J* = 6.2), 7.78 (t, 1 H, *J* = 7.5)	—	4.61 (d, *J* = 8.2)	3.98 (s, 2 H)	1.25 (t, 3 H, Me), 4.20 (q, 2 H, OCH_2)	9.26 (t, *J* = 8.2)
7	131—134	1620, 1680, 1750	2620—3010, 3240	—	7.31—7.52 (m, 7 H), 7.59 (q, 1 H, *J* = 6.2), 7.80 (t, 1 H, *J* = 6.2)	—	4.68 (d, *J* = 9.0)	4.10 (s, 2 H)	5.26 (s, 2 H, OCH_2), 7.31—7.52 (m, 7 H, Ar)	9.32 (t, *J* = 9.0)
9	153—157	1680, 1750	2670—3000, 3280—3285	1520, 1540	8.21 (d, 2 H, *J* = 8.5), 8.38 (d, 2 H, *J* = 8.5)	1.55 (d, 3 H, Me, *J* = 7.0)	4.67 (d, *J* = 9.0)	4.29 (q, *J* = 7.0)	3.71 (s, 3 H, Me)	10.10 (t, *J* = 9.0)
10	160—165	1670—1695, 1750	2600—3060, 3280	1550	8.20 (d, 2 H, *J* = 8.0), 8.35 (d, 2 H, *J* = 8.0)	3.12 (dd, 2 H, CH_2, J_1 = 13.5, J_2 = 8.3), 7.19—7.40 (m, 5 H, Ph)	4.61—4.75 m	4.43 (dd, J_1 = 5.5, J_2 = 3.7)	3.56 (s, 3H, Me)	10.10 (t, *J* = 9.0)
11	95—98	1680, 1750	2680—2980, 3260	1535	8.20 (d, 2 H, *J* = 8.0), 8.30 (d, 2 H, *J* = 8.0)	0.93 (d, 3 H, Me, *J* = 7.0), 1.05 (d, 3 H, Me, *J* = 7.0), 2.45 (m, 1 H, CH)	4.55—4.70 m	4.10 (d, *J* = 3.0)	3.75 (s, 3 H, Me)	10.00 (t, *J* = 9.0)
12	149—154	1680, 1750	2690—2970 3255	1535	8.10 (d, 2 H, *J* = 8.0), 8.28 (d, 2 H, *J* = 8.0)	0.81—1.01 (m, 6 H, Me), 1.17—1.39 (m, 1 H, CH_2), 1.39—1.69 (m, 1 H, CH_2), 2.08—2.27 (m, 1 H, CH)	4.51—4.67 m	4.18 (d, *J* = 3.0)	3.68 (s, 3 H, Me)	9.95 (t, *J* = 9.0)
13	142—147	1670, 1750	2980, 3280	—	7.72 (d, 2 H, *J* = 8.5), 7.90 (d, 2 H, *J* = 8.5)	1.52 (d, 3 H, Me, *J* = 7.0)	4.51—4.72 m	4.12 (q, *J* = 7.0)	3.72 (s, 3 H, Me)	9.82 (t, *J* = 9.0)
15	144—149	1680, 1750	2600—2950, 3280	—	—	—	4.63 (d, *J* = 8.0)	3.95 (s, 2 H)	3.75 (s, 3 H, Me)	9.95 (t, *J* = 9.0)
16	97—101	1680, 1740	2720—2980, 3260	—	8.10 (s, 1 H), 8.65—9.10 (m, 2 H), 9.20—9.65 (m, 1 H)	—	4.62 s	4.10 (s, 2 H)	3.70 (s, 3 H, Me)	10.55 m

* For compounds **5—7**. ** For compounds **9—16**.

Table 5. Yields, melting points, and the results of elemental analysis of *N*-(*p*-nitrobenzamidomethyl)-α-amino acid methyl esters (**28—32**)

Compound	Molecular formula	Found / Calculated (%)			Yield (%)	M.p. /°C
		C	H	N		
28	$C_{12}H_{15}N_3O_5$	58.13 57.82	6.34 6.07	16.55 16.86	41	108—109.5
29	$C_{18}H_{19}N_3O_5$	60.89 60.50	5.71 5.36	11.48 11.76	16	84.5—86
30	$C_{14}H_{19}N_3O_5$	54.54 54.36	6.00 6.19	13.27 13.58	12	99—102
31	$C_{15}H_{21}N_3O_5$	56.23 55.72	6.76 6.55	12.71 13.00	19	76—81
32	$C_{11}H_{13}N_3O_5$	49.58 49.44	4.82 4.90	15.59 15.72	56	111—113

like the reaction of ester **12** with TsCl, these reactions were not accompanied by the destruction of the $N—CH_2—N$ fragment. Compounds **28—43** were characterized by the IR and NMR spectra and elemental analysis.

The ^1H NMR spectra of compounds **9—13**, **21—26**, **28—31**, **36**, and **37**, which contain substituents at the α position with respect to the ethoxycarbonyl group, are, generally, complicated, which is caused by the diastereotopism of the protons of the methylene group of the $N—CH_2—N$ fragment and by the hindered rotation about the C—N bonds of the amide groups.[6] The signals of the α-methine protons of compounds **18** and **31** obtained from enantiomerically pure L-isoleucine are doublets with coupling constants of 10.0 and 6.0 Hz, respectively. When the spin-spin interaction with the methine protons of the isobutyl group is suppressed, the above-mentioned signals degenerate into singlets, which is indicative of the diastereomeric and, hence, enantiomeric purity of compounds **18** and **31**, and provides evidence that the chiral centers are retained in the course of the reactions.

Experimental

The IR spectra of solid compounds were recorded on a Specord-75-IR instrument using KBr pellets. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer in DMSO-d_6, acetone-d_6, and $CDCl_3$ at frequencies of 300.13 (^1H) and 75.5 (^{13}C) MHz. Chemical shifts of the ^1H and ^{13}C signals were measured relative to DMSO-d_6 (δ, 2.50 and 39.5), acetone-d_6 (δ, 2.07 and 30.00), and $CDCl_3$ (δ, 7.27 and 76.9). TLC was carried out on Silpearl UV-250 Silica gel.

***N*-(Amidomethyl)-α-amino acid ester hydrochlorides (5—7 and 9—16).** A mixture of amide (1.2 mmol), α-amino acid ester hydrochloride (1.2 mmol), paraformaldehyde (1.4 mmol), *p*-toluenesulfonic acid monohydrate (0.01 g), and dimethylformamide (5 mL) was carefully heated until a homogeneous solution formed (10—15 min). Then the reaction mixture was cooled and kept at ~20 °C for 12 h. The precipitates of products **5—7**, **9—10**, **12—13**, and **15** were filtered off, thoroughly washed with ether (2—5 mL), and dried under an air

Table 6. ^1H NMR data of *N*-(*p*-nitrobenzamidomethyl)-α-amino acid methyl esters (**28—32**)

Compound	^1H NMR, δ (*J*/Hz)					
	C_6H_4	R^1	NCH_2N	NCHC (NCH_2C)	OMe	NH
28	8.10 (d, 2 H, *J* = 8.5), 8.30 (d, 2 H, *J* = 8.5)	1.23 (d, 3 H, Me, *J* = 6.0)	4.33 (dd, 1 H, J_1 = 12.5, J_2 = 5.5), 4.42 (dd, 1 H, J_1 = 12.5, J_2 = 5.5)	3.55 (q, *J* = 6.0)	3.57 s	8.47 br.s
29	7.96 (d, 2 H, *J* = 8.0), 8.20 (d, 2 H, *J* = 8.0)	2.82 (dd, 1 H, CH_2, J_1 = 10.5, J_2 = 7.0), 2.90 (dd, 1 H, CH_2, J_1 = 10.5, J_2 = 5.0), 7.02—7.22 (m, 5 H, Ph)	4.23 (d, *J* = 5.0)	3.67 (t, *J* = 5.5)	3.45 s	8.75 (t, *J* = 5.0)
30	7.97 (d, 2 H, *J* = 8.5), 8.18 (d, 2 H, *J* = 8.5)	0.85 (d, 6 H, Me, *J* = 5.0) 1.72—1.90 (m, 1 H, CH)	4.16 (dd, 1 H, J_1 = 12.5, J_2 = 5.5), 4.22 (dd, 1 H, J_1 = 12.5, J_2 = 5.5)	3.10 (d, *J* = 6.0)	3.47 s	8.49 (t, *J* = 5.5)
31	8.10 (d, 2 H, *J* = 8.5), 8.30 (d, 2 H, *J* = 8.5)	0.79—0.92 (m, 6 H, Me) 1.07—1.23 (m, 1 H, CH_2) 1.42—1.57 (m, 1 H, CH_2) 1.57—1.72 (m, 1 H, CH)	4.28 (dd, 1 H, J_1 = 13.0, J_2 = 6.0), 4.44 (dd, 1 H, J_1 = 13.0, J_2 = 6.0)	3.42 (d, *J* = 6.0)	3.50 s	8.35 (t, *J* = 6.0)
32	7.62 (d, 2 H, *J* = 9.0), 7.79 (d, 2 H, *J* = 9.0)	—	3.87 (d, *J* = 6.0)	3.00 (s, 2 H)	3.12 s	8.35 (t, *J* = 6.0)

Table 7. Yields, melting points, and the results of elemental analysis of *N*-substituted esters of *N*-(amidomethyl)- and *N*-(imidomethyl)-α-amino acids (**33**—**43**)

Compound	Molecular formula	Found / Calculated (%)			Yield (%)	M.p /°C
		C	H	N		
33	$C_{13}H_{15}N_2O_4F$	55.07 55.32	5.54 5.36	9.66 9.92	60	86—88
34	$C_{14}H_{17}N_2O_4F$	56.98 56.75	5.91 5.78	9.17 9.45	46	Oil
35	$C_{19}H_{19}N_2O_4F$	64.03 63.68	5.26 5.34	7.67 7.28	66	Oil
36	$C_{14}H_{17}N_3O_6$	52.39 52.01	5.22 5.30	12.74 13.00	84	90—95
37	$C_{20}H_{21}N_3O_6$	60.50 60.14	5.31 5.30	10.67 10.52	88	143—148
38	$C_{15}H_{18}N_2O_6$	56.41 55.90	5.82 5.63	8.36 8.69	53	Oil
39	$C_{12}H_{15}N_3O_4$	54.63 54.33	5.56 5.70	16.04 15.84	14	Oil
40	$C_{18}H_{19}N_2O_5SF$	55.02 54.81	5.00 4.86	6.89 7.10	70	118—119
41	$C_{15}H_{15}N_3O_5S_2Cl_2$	40.07 39.83	3.41 3.34	8.98 9.29	55	160—162
42	$C_{16}H_{18}N_2O_5$	60.10 60.37	5.56 5.70	8.99 8.80	19	87—89
43	$C_{22}H_{22}N_2O_5$	67.37 66.99	5.43 5.62	6.85 7.10	78	124—127

stream. Compounds **11** and **16** crystallized when the reaction mass was treated with an ether—acetone mixture. Adduct **14** was isolated as an oil. The yields and physicochemical and spectral characteristics of the compounds obtained are given in Tables 1, 2, and 4.

***N,N*-Bis(*o*-fluorobenzamido)methane (8). a.** One drop of concentrated H_2SO_4 was added with intense stirring to a mixture of *o*-fluorobenzamide (0.2 g, 1.4 mmol), 29% aqueous formalin (0.16 mL), and toluene (5 mL), and then the mixture was rapidly heated to boiling. The solvent was evaporated to half the initial volume, and the mixture was kept at ~20 °C for 12 h. The precipitate that formed was filtered off, washed with acetone, and dried under an air stream. Compound **8** was obtained in a yield of 0.10 g (48 %), m.p. 191—193 °C. ^{1}H NMR (DMSO-d_6) δ: 4.90 (s, 2 H, CH_2); 7.29—7.35 (m, 4 H, C_6H_4); 7.48—7.62 (m, 2 H, C_6H_4); 7.69—7.80 (m, 2 H, C_6H_4). IR (ν/cm^{-1}): 1670; 1750 (CO); 3320 (NH). Found (%): C, 66.74; H, 4.19; N, 10.15. $C_{15}H_{12}N_2O_2F_2$. Calculated (%): C, 66.42; H, 4.46; N, 10.33.

b. A mixture of *o*-fluorobenzamide (0.2 g, 1.4 mmol), paraformaldehyde (0.05 g, 1.66 mmol), glycine ester hydrochloride (1.4 mmol), *p*-toluenesulfonic acid monohydrate (0.01 g), and anhydrous DMSO (0.5 mL) was heated at 60—80 °C until a homogeneous solution formed (10—20 min). Then the mixture was kept at ~20 °C for 24 h, treated with water (2—4 mL), and extracted with ether (5×5 mL). The ether extracts were combined, washed with water, and dried over $MgSO_4$. The solvent was distilled off. A mixture of *N*-hydroxymethyl-*o*-fluorobenzamide and *o*-fluorobenzamide **4** was obtained from the residue by TLC on Silica gel (ethyl acetate was used as the eluent) in a yield of 0.07 g, m.p. 92—96 °C. Acetic anhydride (0.28 mL) and one drop of concentrated H_2SO_4 were added to the mixture obtained, and the mixture was kept at ~20 °C for 48 h. Then water (2—5 mL) was added to the mixture, and the precipitate that formed was filtered off and dried under an air stream. Compound **8** was obtained in a yield of 0.02 g; the

Table 8. ^{1}H NMR data of *N*-substituted esters of *N*-(amidomethyl)- and *N*-(imidomethyl)-α-amino acids (**33**—**43**)

Compound	^{1}H NMR, δ (*J*/Hz)						
	Ar (phthalimido)*	R^1	R (OEt)*	X (Ac)*	NCH_2N	NCHC (NCH_2C)*	NH
33	7.12 (dt, 1 H, J_1 = 12.0, J_2 = 7.5), 7.25 (q, 1 H, *J* = 7.3), 7.41—7.54 (m, 1 H), 7.95—8.08 (m, 1 H)	—	3.71 (s, 3 H, Me)	2.15 (s, 1.8 H), 2.27 (s, 1.2 H)	4.96 (d, 1.2 H, *J* = 6.7), 5.10 (d, 0.8 H, *J* = 6.7)	4.27 (s, 0.8 H), 4.35 (s, 1.2 H)	7.65 (br.s, 0.6 H), 7.79 (br.s, 0.4 H)
34	7.12 (dt, 1 H, J_1 = 12.0, J_2 = 7.5), 7.24 (q, 1 H, *J* = 7.5), 7.41—7.53 (m, 1 H), 7.97 (d, 0.6 H, *J* = 7.5), 8.05 (d, 0.4 H, *J* = 7.5)	—	1.25 (t, 1.8 H, Me), 1.27 (t, 1.2 H, Me), 4.18 (q, 2 H, OCH_2)	2.03 (s, 1.8 H), 2.27 (s, 1.2 H)	4.98 (d, 1.2 H, *J* = 6.7), 5.10 (d, 0.8 H, *J* = 6.7)	4.23 (s, 0.8 H), 4.32 (s, 1.2 H)	7.65 (br.s, 0.6 H), 7.82 (br.s, 0.4 H)
35	7.12 (q, 1 H, *J* = 9.0), 7.25 (q, 1 H, *J* = 8.5), 7.48 (q, 1 H, *J* = 7.5), 7.93—8.10 (m, 1 H)	—	5.18 (s, 1.2 H, CH_2), 5.20 (s, 0.8 H, CH_2), 7.35 (br.s, 5 H, Ph)	2.02 (s, 1.8 H), 2.30 (s, 1.2 H)	5.00 (d, 1.2 H, *J* = 6.0), 5.12 (d, 0.8 H, *J* = 6.0)	4.31 (s, 0.6 H), 4.43 (s, 1.2 H)	7.68 (br.s, 0.6 H), 7.78 (br.s, 0.4 H)

(to be continued)

Table 8 (*continued*)

Compound	^{1}H NMR, δ (*J*/Hz)						
	Ar (phthalimido)*	R^1	R (OEt)*	X (Ac)*	NCH_2N	NCHC (NCH_2C)*	NH
36	7.93 (d, 0.8 H, J = 8.0), 8.00 (d, 1.2 H, J = 8.0), 8.27 (d, 1.2 H, J = 8.0), 8.32 (d, 0.8 H, J = 8.0)	1.50 (d, 1.8 H, Me, J = 7.0) 1.70 (d, 1.2 H, Me, J = 7.0)	3.70 (s, 1.8 H, Me), 3.80 (s, 1.2 H, Me)	2.12 (s, 1.8 H), 2.22 (s, 1.2 H)	5.07 (dd, 1.2 H, J_1 = 13.5, J_2 = 6.0), 5.47 (dd, 0.8 H, J_1 = 13.5, J_2 = 5.0)	4.54 (q, 0.4 H, J = 7.0) 4.95 (q, 0.6 H, J = 7.0)	7.51 (t, 0.4 H, J = 6.0), 8.21 (t, 0.6 H, J = 6.0)
37	7.97 (d, 2 H, J = 7.5), 8.30 (d, 2 H, J = 7.5)	3.17–3.32 (m, 0.8 H,CH_2), 3.39–3.59 (m, 1.2 H,CH_2), 7.11–7.39 (m, 5 H,Ph)	3.75 (s, 1.2 H, Me), 3.83 (s, 1.8 H, Me)	1.89 (s, 1.2 H), 2.15 (s, 1.8 H)	4.92–5.15 (m, 2 H)	4.65–4.76 (m, 1 H),	7.52 (t, 0.4 H, J = 6.0), 7.65 (t, 0.6 H, J = 6.0)
38	2.13 (s, 1.5 H, Me), 2.15 (s, 1.5 H, Me), 6.95 (dd, 1 H, Ar, J_1 = 7.0, J_2 = 1.5), 7.15 (t, 1 H, Ar, J_1 = 7.5, J_2 = 1.5), 7.52 (dd, 1 H, Ar, J_1 = 7.5, J_2 = 1.5), 7.67 (dd, 1 H, Ar, J_1 = 7.5, J_2 = 1.5)	–	3.60 (s, 3 H, Me)	1.89 (s, 1.5 H), 2.21 (s, 1.5 H)	4.75 (d, 1 H, J = 6.5), 4.82 (d, 1 H, J = 6.5)	4.10 (s, 1 H), 4.21 (s, 1 H)	8.34 (t, J = 6.5)
39	7.35–7.48 (m, 1 H), 8.05–8.21 (m, 1 H), 8.70–8.80 (m, 1 H), 9.00–9.15 (m, 1 H)	–	3.72 (s, 3 H, Me)	2.05 (s, 1.8 H), 2.27 (s, 1.2 H)	4.95 (d, 1.2 H, J = 7.2), 5.11 (d, 0.8 H, J = 7.2)	4.28 (s, 0.8 H), 4.40 (s, 1.2 H)	7.95 (t, 0.6 H), 8.04–8.21 (m, 0.4 H)
40	7.22 (t, 1 H, J = 8.0), 7.28 (q, 1 H, J = 8.0), 7.58 (q.d, 1 H, J_1 = 7.9, J_2 = 1.5), 7.76 (dd, 1 H, J_1 = 7.5, J_2 = 1.5)	–	3.64 (s, 3 H, Me)	2.40 (s, 3 H, Me), 7.36 (d, 2 H, Ar, J = 7.5), 7.8 (d, 2 H, Ar, J = 7.5)	5.05 (d, 2 H, J = 6.0)	4.30 (s, 2 H)	7.99 (t, J = 6.0)
41	–	–	3.67 (s, 3 H, Me)	2.43 (s, 3 H, Me), 7.41 (d, 2 H, Ar, J = 8.3), 7.81 (d, 2 H, Ar, J = 8.3)	5.08 (d, 2 H, J = 6.0)	4.27 (s, 2 H)	8.48 (t, J = 6.0)
42	7.77–7.80 (m, 2 H), 7.84–7.91 (m, 2 H)	1.47 (d, 3 H, Me, J = 6.9)	0.95 (t, 3 H, Me), 3.91 (q, 2 H, OCH_2)	2.50 (s, 3 H)	5.28 (s, 2 H)	4.21 (q, 1 H, J = 6.9)	–
43	7.74 (br.s, 4 H)	3.27 (d, 1 H, CH_2, J = 12.0), 3.42 (dd, 1 H, CH_2, J_1 = 12.0, J_2 = 10.5) 6.79–7.13 (m, 5 H, Ph)	1.05 (t, 3 H, Me), 4.08 (q, 2 H, OCH_2)	2.50 (s, 3 H)	4.73 (d, 1 H, J = 14.0), 4.96 (d, 1 H, J = 14.0)	4.10–4.25 (m, 1 H)	–

* For compounds **42** and **43**.

compound obtained was identical to the product prepared by the method described above.

***N,N*-Bis(*p*-bromobenzamidomethyl)glycine methyl ester (17).** NaOH (0.02 g, 0.05 mmol) and 29% aqueous formalin (0.09 mL, 0.96 mmol) were added successively with stirring to a boiling solution of glycine methyl ester hydrochloride (0.06 g, 0.48 mmol) and *p*-bromobenzamide (0.19 g, 0.96 mmol) in Pr^{i}OH (5 mL). The reaction mixture was cooled and kept at ~20 °C for 24 h. The NaCl precipitate was filtered off, and the solvent was removed from the filtrate *in vacuo*. The residue crystallized when treated with ether. Compound **17** was obtained in a yield of 0.16 g (67 %), m.p. 118—122 °C. ^{1}H NMR (acetone-d_6) δ, *J*/Hz: 3.64 (s, 3 H, OMe); 3.72 (s, 2 H, NCH_2C); 4.59 (d, 4 H, NCH_2N, J = 6.0); 7.64 (d, 4 H, C_6H_4, J = 8.5); 7.85 (d, 4 H, C_6H_4, J = 8.5); 8.71 (br.s, 2 H, NH). IR (ν/cm^{-1}): 1645; 1670; 1745 (CO); 3280; 3300 (NH). Found (%): C, 43.80; H, 3.90; Br, 31.70; N, 8.00. $C_{19}H_{19}Br_2N_3O_4$. Calculated (%): C, 44.40; H, 3.70; Br, 31.20; N, 8.20.

***N,N*-Bis(*p*-nitrobenzamidomethyl)-L-isoleucine (18) methyl ester and *N*-(*p*-nitrobenzamidomethyl)-L-isoleucine methyl ester (31).** A mixture of hydrochloride **12** (0.2 g, 0.55 mmol), tosyl chloride (0.21 g, 1.10 mmol), and dry pyridine (1 mL) was stirred at −10 °C for 1 h. The reaction mass was kept at 20 °C for 48 h, diluted with cold water (4—5 mL), and carefully acidified with HCl (diluted) to pH ~ 2. The aqueous solution was extracted with chloroform. The organic phase was washed with water and dried over $MgSO_4$. Compound **18** was isolated by TLC on Silica gel (a 1 : 1 benzene—ether mixture was used as the eluent) in a yield of 0.02 g (21 %), m.p. 127—135 °C, R_f = 0.34. ^{1}H NMR ($CDCl_3$) δ, *J*/Hz: 0.82—1.00 (m, 6 H, Me); 1.12—1.32 (m, 1 H, CH_2); 1.62—1.86 (m, 1 H, CH_2); 1.92—2.10 (m, 1 H, CH); 3.37 (d, 1 H, NCHC, J = 10.0); 3.61 (s, 3 H, OMe); 4.50 (d.d, 2 H, NCH_2N, J_1=13.5; J_2 = 6.0); 4.69 (d.d, 2 H, NCH_2N, J_1 = 13.5; J_2 = 7.5); 7.90 (t, 2 H, J = 7.00); 8.03 (d, 4 H, C_6H_4, J = 8.5); 8.42 (d, 4 H, C_6H_4, J = 8.5). ^{13}C NMR (DMSO-d_6) δ: 10.2 (Me); 15.6 (Me); 25.0 (CH_2); 33.8 (CH); 51.6, (NCHC); 55.2 (NCH_2N); 68.7 (OMe); 123.7; 128.2 (Ar, CH); 139.3 (CCO); 149.8 (CNO_2); 165.8 (CONH); 176.5 (CO). Found (%): C, 56.11; H, 5.67; N, 13.62. $C_{23}H_{27}N_5O_8$. Calculated (%): C, 55.09; H, 5.43; N, 13.96. Compound **31** was isolated by TLC on Silica gel (a 1 : 1 benzene—ether mixture was used as the eluent) in a yield of 0.03 g (19 %), m.p. 76—81 °C, R_f = 0.25. ^{13}C NMR (DMSO-d_6) δ: 11.0 (Me); 16.0 (Me); 26.0 (CH_2); 39.6 (CH); 51.8 (NCHC); 55.9 (NCH_2N); 64.7 (O); 124.5; 129.5 (Ar, CH); 141.4 (CCO); 150.6 (CNO_2); 166.2 (CONH); 176.4 (CO). Found (%): C, 56.23; H, 6.76; N, 12.71. $C_{15}H_{21}N_3O_5$. Calculated (%): C, 55.72; H, 6.55; N, 13.00.

***N,N*-Bis(benzotriazolylmethyl)glycine methyl ester (19).** Sodium acetate trihydrate (0.13 g, 0.95 mmol) and 29% aqueous formalin (0.18 mL, 1.9 mmol) were added successively to a boiling solution of glycine methyl ester hydrochloride (0.12 g, 0.95 mmol) and 1,2,3-benzotriazole (0.22 g, 1.9 mmol) in Pr^{i}OH (5 mL). The reaction mixture was boiled for 2 min and then was poured into ice water (7 mL). The mixture was extracted with chloroform (3×7 mL). The extract was washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo*. The residue crystallized upon treatment with cold ether. Compound **19** was obtained in a yield of 0.07 g (11 %), m.p. 116—119 °C. ^{1}H NMR (acetone-d_6) δ: 3.49 (s, 3 H, OMe); 3.95 (s, 2 H, NCH_2C); 5.95 (s, 4 H, NCH_2N); 7.39—7.58 (m, 4 H, C_6H_4); 7.83—8.07 (m, 4 H, C_6H_4). IR (ν/cm^{-1}): 1735 (CO); 3200 (NH).

***N*-(Imidomethyl)-α-amino acid esters (21—26).** Sodium acetate trihydrate (1.39 mmol) (in the case of hydrochloride) and 29% aqueous formalin (0.19 mL, 17.9 mmol) were added with stirring to a boiling solution of α-amino acid ester or its hydrochloride (1.39 mmol) and imide (1.39 mmol) in Pr^{i}OH. The reaction mass was kept at ~20 °C for 12 h. Then NaCl was filtered off, and the solvent was removed *in vacuo*. Compounds **21** and **24** crystallized when treated with ether. Compounds **22**, **25**, and **26** are oily compounds; they did not crystallize upon storage. With the aim of identifying these compounds, they were transformed to hydrochlorides by treatment with concentrated HCl (0.14 mL) in $CHCl_3$. The yields, melting points, and data of the IR and ^{1}H NMR spectra of compounds **21—26** are given in Table 3.

***N*-(Phthalimidomethyl)phenylalanine ethyl ester (24).** A solution of phenylalanine ethyl ester (0.21 g, 1.13 mmol) in THF (0.5 mL) was added to a boiling solution of *N*-hydroxymethylphthalimide **20** (0.2 g 1.13 mmol) in Pr^{i}OH (5 mL). The reaction mixture was kept at ~20 °C for 12 h. The solvent was removed *in vacuo*. The residue crystallized when treated with ether. Compound **24** was obtained in a yield of 17 g (43 %).

***N*-(*p*-Nitrobenzamidomethyl)-α-amino acid methyl esters (28—30 and 32).** A 45% aqueous NaOH solution (0.26 mL, 0.44 mmol) was added dropwise to a suspension of **9—11** or **27** (0.4 mmol) in water (5 mL), and the mixture was stirred until the base was completely neutralized (12—24 h). The precipitate was filtered off, washed with water and ether, and dried under an air stream. The yields and the spectral characteristics of compounds **28—30** and **32** are given in Table 5. ^{13}C NMR of compound **30** (DMSO-d_6) δ: 17.9 (Me); 18.7 (Me); 31.2 (CH); 50.9 (NCHC); 54.5 (NCH_2N); 64.1 (OMe); 122.9; 128.3; 139.5 (Ar, CH); 164.9 (CONH); 175.0 (CO).

***N*-Sulfonyl-*N*-(amidomethyl)glycine esters (40 and 41).** A mixture of hydrochloride **5** or **15** (0.193 mmol), TsCl (0.38 mmol), and dry pyridine (0.4 mL) was stirred at −10 °C for 1 h and kept at ~20 °C for 48 h. Then the mixture was diluted with cold water (1—2 mL), carefully acidified with HCl (diluted) to pH ~ 2. The precipitate was filtered off, washed with water, and dried under an air stream. Compounds **40** and **41** were isolated by TLC on Silica gel (a 1 : 1 benzene—ether mixture was used as the eluent). The melting points, yields, and spectral characteristics are given in Tables 7 and 8. ^{13}C NMR of compound **41** (acetone-d_6) δ: 21.4 (Me); 48.5 (NCHC); 52.4 (OMe); 53.4 (NCH_2N); 128.1; 130.6; 144.7 (Ar, CH); 131.6 (CCONH); 138.5 (CMe); 147.8 (N=CCl); 154.7 (SCCl); 161.5 (CONH); 169.9 (CO).

***N*-Acetyl-*N*-(amidomethyl)- and *N*-acetyl-*N*-(imidomethyl)-α-amino acid esters (33—39 and 42—43).** A mixture of compound **5—7**, **9**, **10**, **14**, **16**, **23**, or **24** (2.5 mmol), acetic anhydride (0.1 mmol), and $NaHCO_3$ (7.5 mmol) was stirred for 1 h and then kept at ~20 °C for 3 days. Then water (5—7 mL) was added, and the aqueous solution was extracted with chloroform (5×5 mL). The combined organic extracts were washed with water and dried over $MgSO_4$. Compounds **37** and **43** crystallized when treated with ether (3—4 mL). Compounds **33—36**, **38**, **39**, and **42** were isolated by TLC on Silica gel (for compounds **33—36**, **38**, and **39**, ethyl acetate was used as the eluent, for **42**, a 1 : 1 benzene—ether mixture was used as the eluent). The ^{1}H NMR data, the yields, and the melting points of compounds **33—39** and **42—43** are given in Tables 7 and 8. ^{13}C NMR of compound **37** ($CDCl_3$) δ: 21.7 (MeC); 35.0 and 35.8 (CH_2Ph); 49.5 and 53.9 (NCH_2N); 53.0 (Me); 59.8 and 62.8 (CH); 123.9; 128.9; 138.8; 139.5 (Ar, CH); 149.9 (CNO_2); 127.2; 128.3; 128.7; 136.8 (Ph); 164.6; 170.6; 172.1; 173.5 (C=O).

References

1. S. G. Zlotin, I. V. Sharova, and O. A. Luk'yanov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1078 [*Russ. Chem. Bull.*, 1994, **43**, 1015 (Engl. Transl.)].
2. S. G. Zlotin, I. V. Sharova, and O. A. Luk'yanov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1306 [*Russ. Chem. Bull.*, 1995, **44**, 1260 (Engl. Transl.)].
3. S. G. Zlotin, I. V. Sharova, and O. A. Luk'yanov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1299 [*Russ. Chem. Bull.*, 1995, **44**, 1252 (Engl. Transl.)].
4. P. K. Dabral, R. Chandra, and M. C. Sharma, *Indian J. Microbiol.*, 1981, **21**, 109.
5. A. Einhorn, E. Bischkopff, C. Ladisch, T. Manermayer, G. Schupp, E. Sprongerts, and B. Bzelinski, *Lieb. Ann. Chem.* 1905, **343**, 207.
6. H. Gunter, NMR *Spectroscopy. Introduction*, John Wiley and Sons, XIV, 1980.

Received November 14, 1995;
in revised form March 6, 1996